ISSN 1561-8641 (print)
ISSN 2658-7327 (online)
ISSN 2713-3265 (english)

THE OFFICIAL JOURNAL OF THE RUSSIAN SCIENTIFIC SOCIETY OF CLINICAL ELECTROPHYSIOLOGY, ARRHYTHMOLOGY AND CARDIAC PACING

4 2024

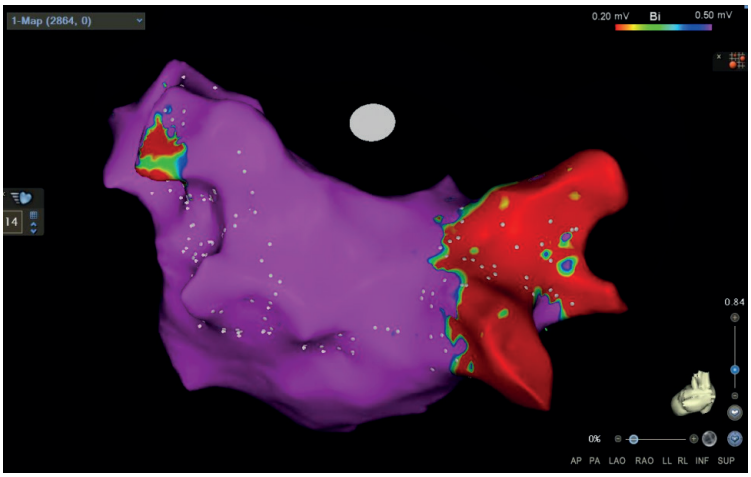

Figure from the article by T.V.Moskovskih, A.V.Smorgon, S.Yu.Usenkov et al.

JOURNAL of Arrhythmology

Website: https://vestar.elpub.ru
Included in the List of publications recommended by the expert council of the Higher Attestation Commission
Subscription index of the Rospechat catalog: PM033

JOURNAL OF ARRHYTHMOLOGY

A PEER-REVIEWED SCIENTIFIC JOURNAL

Volume 31 No 4 (118) 2024

Founded in 1993

The journal was registered by the Committee of the Russian Federation for Press № 016512 on August 13, 1997.
Periodicity - 4 issues per year. **Subscription index of the Russian Post catalog:** PM033.

The Journal is listed by the Scopus, Supreme Examination Board (VAK), indexed by the Russian Science Citation Index (RSCI core). Two-year RSCI impact factor: 0.403. Electronic version: https://vestar.elpub.ru, www.vestar.ru, www.elibrary.ru.
DOI prefix: 10.35336.

Editorial office address: 197341, St. Petersburg, 2 Akkuratova str. E-mail: vestnik_aritmologii@mail.ru.
Put in the set on 25/10/2024. Signed in print 16/11/2024.
Printing house address: 198320, St. Petersburg, Krasnoe Selo, ul. Svobody, 57.
Coated paper 110 g/m^2, format 60x90 1/8. Offset printing. Conditional printed sheets 9.0. Order. edition 3000 copies.

Publishing House NAO «Institute of Cardiology Technic».
Publishing License LR No. 065572 issued by the Press Committee of the Russian Federation on December 16, 1997
Publishing house address: 194214 St. Petersburg, Vyborgskoye sh., 22A, NAO «INCART»

Founders

Almazov National Medical Research Centre, 2. Akkuratova str., 197341 St. Petersburg
NP «St. Petersburg Cardiology Society», 2. Akkuratova str., 197341 St. Petersburg
NAO «Institute of Cardiology Technic», 22A Vyborgskoye shosse, 194214 St. Petersburg

CONTENT

https://doi.org/10.35336/VA-1280

COMPARATIVE ANALYSIS OF ENDOCRINE PROFILE AND FIVE-YEAR SURVIVAL OF CARDIAC RESYNCHRONIZATION THERAPY MALE RESPONDERS RESIDING IN CONDITIONS OF THE FAR NORTH AND SOUTH OF TYUMEN REGION

T.N.Enina, T.I.Petelina, N.E.Shirokov, I.A.Repina, L.I.Gapon

Tyumen Cardiology Research Center, Tomsk National Research Medical Center of the Russian Academy of Sciences, Russia, Tyumen, 111 Melnikayte str.

Aim. To evaluate endocrine profile, biomarkers of heart failure, 5-year survival of cardiac resynchronization therapy (CRT) male responders living in the Far North (FN) and the south of Tyumen region (sTr).

Methods. Fifty-six CRT male responders (with decrease of left ventricular end-systolic volume >15% in November 2020) under the age of 65 (55.0±7.8 years old) were divided into 2 groups: 1(n=23) - FN patients; 2 (n=33) - sTr. Echocardiography (Echo), thyroid-stimulating hormone (TSH), triiodothyronine (fT3), thyroxine (fT4), parathyroid hormone (PTH), cortisol (CORT), testosterone (TES), estradiol (E2), dihydroepiandrosterone sulfate (DHEAS), progesterone (PGN), adrenaline (Adr), norepinephrine (NAdr), interleukins (IL) 6, 10, tumor necrosis factor (TNF-α), C-reactive protein (CRP), NT-proBNP, myeloperoxidase (MPO), matrix metalloproteinase (MMP-9), tissue inhibitor of metalloproteinases (TIMP-1) were assessed. Relationship of hormones with Echo, biomarkers was evaluated by Spearman method, 5-year survival - by Kaplan-Meier method, and association of lastmentioned with studied factors - by Cox regression.

Results. Radiofrequency ablation of atrioventricular junction (RFA AVJ) were differed in groups (47.8 vs 21.2%; p=0.036). At the initial stage, in group 1, right ventricle, Adr, TNF-α, CRP, TIMP-1, CORT, TSH, fT4 were greater, fT3/fT4 was lower. In groups, reverse cardiac remodeling was revealed in dynamics; decrease of TIMP-1, PGN in Gr1; decrease of NT-proBNP, TIMP-1, MPO, PGN, increase of TES, E2, TNF-α in Gr2,. Positive associations of TSH, PTH and negative - DHEAS with Echo; positive connections between PGN, CORT and MMP-9; TES with NAdr; E2 with IL-10 were registered. Five-year survival rate was 80.7% vs 83.4% (Log Rank test=0.724), associated with IL-6 level in northerners.

Conclusion. Multihormonal imbalance, manifested by greater levels of CORT, TSH, fT4, lower values of fT3/fT4, accompanied by sympatho-adrenal, immune activation, fibroformation imbalance, higher power of RFA AVJ, indicates greater severity of heart failure, tension of adaptive mechanisms in CRT male responders of FN. CRT modulating effects in groups contributed to comparable 5-year survival associated with level of IL-6 in northerners.

Key words: chronic heart failure; cardiac resynchronization therapy; endocrine imbalance; survival; the Far North

Conflict of Interests: none.
Funding:none.
Received: 03.11.2023 **Revision Received:** 23.07.2024 **Accepted:** 06.10.2024
Corresponding author: Tatyana Enina, E-mail: E-mail: enina@infarkta.net

T.N.Enina - ORCID ID 0000-0002-7443-2952, T.I. Petelina - ORCID ID 0000-0001-6251-4179, N.E. Shirokov - ORCID ID 000-0002-4325-2633, L.I.Gapon - ORCID ID 0000-0002-3620-0659

For citation: Enina TN, Petelina TI, Shirokov NE, Repina IA, Gapon. Comparative analysis of endocrine profile and five-year survival of cardiac resynchronization therapy male responders residing in conditions of the Far North and south of Tyumen region. *Journal of Arrhythmology*. 2024; 31(4): 5-16. https://doi.org/10.35336/VA-1280.

Chronic heart failure (CHF) is a global health challenge due to its high prevalence and continuous growth. The estimated global incidence of CHF is 64.3 million cases[1]. Epidemiological studies in the Russian Federation over 20 years indicate an increase in CHF prevalence from 6.1% to 8.2% for functional classes I-IV and from 1.8% to 3.1% for classes III-IV[2]. A critical factor in the complex pathogenesis of CHF is endocrine imbalance[3], which is associated with sympatho-adrenal[4] and immune activation[5], as well as increased fibroformation[6].

The expansion of economic activities in the Arctic has heightened scientific interest in the impact of Arctic climatic conditions on the development of various diseases. Previous studies have established that residing in the Far North (FN) for over four years contributes to the early onset of coronary atherosclerosis [7] and arterial hypertension[8]. CHF, as the culmination of the cardiovascular continuum, is currently managed using cardiac resynchronization therapy (CRT). We hypothesize that the adverse climatic conditions of the Far North influence changes in hormonal systems involved in cardiac homeostasis, leading to specific patterns of CHF development and progression. However, these patterns are not yet documented in the scientific literature, underlining the relevance of our study.

Aim: To perform a comparative analysis of the endocrine profile (thyroid and parathyroid hormones, cortisol, sex hormones), biomarkers of immune, sympatho-adrenal, and neurohumoral systems, fibroformation, and five-year survival of male CRT responders living in the Far North and the south of the Tyumen region (sTr).

METHODS

To eliminate the influence of gender and age on the analysis of the endocrine profile and to create a homogeneous group, the study included 56 male CRT responders (defined by a reduction in left ventricular end-systolic volume [LVESV] >15% from baseline at the endpoint in November 2020) under the age of 65 (55.0±7.8 years). These participants resided in the Far North (FN, n=23) in the Yamalo-Nenets Autonomous Okrug (YNAO) and in the south of the Tyumen region (sTr, n=33). They were recruited from the "Registry of Performed CRT Procedures" (State Database Registration Certificate No. 2010620077 dated February 1, 2010). Ischemic CHF was diagnosed in 26 men (46.4%), and CRT devices with a defibrillator function were implanted in 34 (60.7%) patients. Informed consent was obtained from all participants, and the study was approved by the ethics committee.

Patient evaluations were conducted at baseline, after 1, 3, and 6 months, and then every subsequent 6 months post-CRT implantation. For this analysis, data from the baseline and the final visit (November 2020) were included. For deceased patients, data collected prior to their death were used.

Echocardiography (Echo) was performed using a Philips IE-33 system (USA) to assess standard parameters. Left ventricular ejection fraction (LVEF) was measured using Simpson's method. Plasma levels of adrenaline (Adr), norepinephrine (NAdr), myeloperoxidase (MPO), matrix metalloproteinase 9 (MMP-9), and tissue inhibitor of metalloproteinase 1 (TIMP-1) were assessed via solid-phase enzyme-linked immunosorbent assay (ELISA), with optical density measured using a StatFax 4200 reader (USA). Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), interleukins (IL) 6 and 10, tumor necrosis factor α (TNF-α), total testosterone (TES), progesterone (PGN), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2), cortisol (CORT), intact parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) were analyzed using a solid-phase chemiluminescent immunoassay on an IMMULITE 1000 analyzer (Siemens Diagnostics, USA). High-sensitivity C-reactive protein (CRP) levels in serum were determined using analytical kits from Roche Diagnostics GmbH on a COBAS INTEGRA 400 Plus analyzer (Roche Diagnostics GmbH, Germany).

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 23 software package. For data with a normal distribution, assessed using the Kolmogorov-Smirnov test, results were presented as M±sd, where M is the mean and sd is the standard deviation. For data with a non-normal distribution, results were presented as the median (Me) with interquartile range (IQR) as the 25th and 75th percentiles. Qualitative variables were analyzed using the χ^2 test. For quantitative data in unrelated groups, Student's t-test was applied for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data.

Spearman's method was used to assess correlations between hormone levels and Echo parameters and biomarkers. Kaplan-Meier survival analysis was utilized to evaluate survival rates. Cox regression analysis (univariate and multivariate) was applied to identify factors associated

Table 1.

Clinical characteristics of the studied groups

Indicator	Group I FN (n=23)	Group II sTr (n=33)	p between groups
MSP, months	74.5 [34.3;107.0]	63.0 [42.0;100.0]	0.690
Age, years	55.9±5.4	54.4±9.1	0.668
CRT-D, n (%)	14 (60.9)	20 (60.6)	0.984
CAD, n (%)	9 (39.1)	17 (51.5)	0.361
PICS, n (%)	6 (26.1)	7 (21.2)	0.671
CABG, n (%)	1 (4.3)	0 (0)	0.227
PCI, n (%)	6 (26.1)	7 (21.2)	0.671
NYHA FC I, n (%)*	0 / 4 (17.4)	0 / 12 (36.4)	0.888 / 0.461
NYHA FC II, n (%)	15 (65.2) / 15 (65.2)	24 (72.7) / 17 (51.5)	
NYHA FC III, n (%)	7 (30.5) / 3(13.1)	7 (21.2) / 3(9.1)	
NYHA FC IV, n (%)	1 (4.3) / 1 (4.3)	2 (6.1) / 1 (3.0)	
p within the group	0.502	0.075	
HTN, n (%)	17 (73.9)	24 (72.7)	0.921
AF, n (%)	14 (60.9)	15 (45.5)	0.202
AVJ RFA, n (%)	11 (47.8)	7 (21.2)	0.036
DM, n (%)	3 (13.0)	3 (9.1)	0.639
Obesity, n (%)	10 (43.5)	17 (51.5)	0.551
BMI, kg/m^2	29.4±6.3	29.9±6.0	0.696
QRS duration, ms	132.1±40.8	148.0±40.2	0.325
LBBB, n (%)	8 (34.8)	20 (60.6)	0.057

Note: hereinafter, FS - Far North; sTr - southern Tyumen region; MSP - mean observation period; CRT-D - cardiac resynchronization therapy device with defibrillator function; CAD - coronary artery disease; PICS - post-infarction cardiosclerosis; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; NYHA FC - New York Heart Association functional class of heart failure; * - data dynamics indicated with a slash; HTN - arterial hypertension; AF - atrial fibrillation; AVJ RFA - atrioventricular junction radiofrequency ablation; DM - diabetes mellitus; BMI - body mass index; LBBB - left bundle branch block.

with survival. A p-value of <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the studied patients are presented in Tables 1 and 2. Patients were comparable in terms of baseline clinical parameters, except for a higher frequency of atrioventricular junction radiofrequency ablation (RFA AVJ) in Group 1. In Group 1, there was no significant change in NYHA functional class dynamics, which might be attributed to the small sample size or clinical features of the patients. In contrast, Group 2 demonstrated a trend (p=0.075) towards improvement in NYHA functional class. Initially, there were no differences in the prescription frequency of major drug groups between the groups. However, during follow-up, Group 1 showed a higher frequency of calcium channel blockers (amlodipine, felodipine), likely due to a greater need for blood pressure control. Additionally, Group 1 showed an increased frequency of statin prescriptions, likely reflecting more diligent outpatient monitoring of patients with CRT devices. The frequency of statin use in Group 2 remained unchanged.

Changes in exercise tolerance based on the six-minute walk test and Echo parameters are shown in Table 3. Initially, Group 1 had larger right ventricle sizes. CRT therapy in both groups resulted in favorable and consistent Echo parameter dynamics. However, Group 1 exhibited smaller left ventricular (LV) end-diastolic diameter and end-systolic volume. Only Group 2 showed a significant improvement in exercise tolerance.

Biomarker dynamics are detailed in Table 4. Initially, Group 1 showed higher levels of adrenaline, TNF-α, and CRP. TIMP-1 and MMP-9 levels were elevated in both groups, reflecting the severity of the disease and fibroformation imbalance. There were no differences in MMP-9 levels between groups, but Group 1 exhibited higher TIMP-1 levels. MPO levels were within reference values in both groups. Over time, Group 1 showed a reduction in TIMP-1 levels, while Group 2 experienced increases in norepinephrine and TNF-α, alongside decreases in MPO, NT-proBNP, and TIMP-1.

Hormone dynamics are presented in Table 5. Average levels of testosterone, estradiol, and progesterone in both groups were within reference ranges. There were no differences in sex hormone levels between groups. Initially, DHEAS levels were below reference ranges in both groups. Despite no significant changes in DHEAS levels during follow-up, final values were within reference ranges. Only Group 2 showed increases in testosterone and estradiol over time. Both groups demonstrated reductions in progesterone levels, associated with heart remodeling during CRT therapy. Cortisol levels were within reference ranges across all time points, with higher initial levels in Group 1. No significant changes in cortisol levels were observed in either group. Baseline parathyroid hormone (PTH) levels in Group 1 and follow-up levels in Group 2 exceeded reference ranges, with a tendency for higher PTH levels in Group 2. No significant changes in PTH levels were observed during follow-up.

Thyroid hormone levels (TH) were within reference ranges across all time points in both groups. Group 1 had higher initial TSH and free T4 levels and lower T3/T4 ratios. Among three patients from YNAO, TSH levels were above normal in two patients and below normal in one. Thyroid abnormalities were managed appropriately. During follow-up, TSH levels in all YNAO patients normalized, reflecting the effectiveness of medical management. No significant changes in TH levels were observed in either group during CRT therapy. Correlations be-

Table 2.

Drug therapy in the study groups

Indicator	Group I FN (n=23)	Group II sTr (n=33)	p between groups
AAD, n (%)	6 (26.1) / 8 (34.8)	9 (27.3) / 11 (33.3)	1.000 / 0.910
p within group	0.625	0.625	
MRA, n (%)	16 (69.6) / 18 (78.3)	29 (87.9) / 27 (81.8)	0.154 / 0.742
p within group	1.000	0.625	
Diuretics, n (%)	11 (47.8) / 18 (78.3)	18 (54.5) / 31 (93.9)	0.741 / 0.081
CCA, n (%)	6 (26.1) / 10 (43.5)	8 (24.2) / 8 (24.2)	0.800 / 0.039
p within group	0.125	1.000	
BB, n (%)	19 (82.8) / 19 (82.8)	31 (93.9) / 27 (81.8)	0.338 / 0.939
p within group	1.000	0.125	
Digoxin, n (%)	9 (39.1) /6 (26.1)	9 (27.3) / 8 (24.2)	0.291 / 0.875
p within group	0.453	1.000	
Anticoagulants, n (%)	10 (43.5) / 12(52.2)	16 (48.5) / 15 (45.5)	0.825 / 0.621
p within group	1.000	1.000	
Antiplatelets, n (%)	9 (39.1) / 8 (34.8)	16 (48.5) /14 (42.4)	0.580 / 0.565
p within group	0.500	0.625	
ACEI, n (%)	20 (87.0) / 17 (73.9)	26 (78.8) / 23 (69.7)	1.000 / 0.731
p within group	0.125	0.375	
ARB, n (%)	2 (8.7) /5 (21.7)	7 (21.2) / 7 (21.2)	0.234 / 0.962
p within group	0.250	1.000	
Statins, n (%)	6 (26.1) / 19 (82.8)	16 (48.5) 21 (63.6)	0.116 / 0.122
p within group	<0.001	0.227	

Note: hereinafter, AAD - Antiarrhythmic drugs (amiodarone, sotalex); MRA - Mineralocorticoid receptor antagonists; CCA - Calcium channel antagonists (amlodipine, felodipine); BB - β-blockers; ACEI - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin receptor blockers.

tween hormone levels, Echo parameters, and biomarkers at the study endpoint are detailed in Table 6.

Kaplan-Meier analysis revealed comparable five-year survival rates between the groups (80.7% vs. 83.4%; Log Rank test=0.724) (Figure 1). Multivariate analysis results are presented in Table 7. In Group 1, univariate analysis showed associations between five-year survival and levels of IL-6, TIMP-1, and NT-proBNP at the study endpoint. However, multivariate analysis identified only IL-6 levels at the study endpoint as being associated with five-year survival. In Group 2, univariate analysis linked survival with Echo parameters (LV end-diastolic and end-systolic volumes, LV ejection fraction) and MMP-9 levels. However, none of these factors were associated with survival in multivariate analysis.

DISCUSSION

The literature highlights the issue of multihormonal imbalance in patients with chronic heart failure (CHF), involving the somatotropic axis (growth hormone and its tissue effector, insulin-like growth factor-1 (IGF-1)) [9], anabolic steroids (testosterone (TES) and dehydroepiandrosterone sulfate (DHEAS)), glucocorticoids (cortisol), and thyroid and parathyroid hormones [3]. Each identified defect is associated with a deterioration in clinical status, functional capacity, and increased mortality [10]. Among the participants of the Italian T.O.S.CA registry (Trattamento Ormonale nello Scompenso CArdiaco; n=480 with LVEF <40%), 77% were diagnosed with multiple hormonal deficiencies, significantly increasing the relative risk of death [HR 2.2 (1.28-3.83), p = 0.01] [11]. In our study, hormonal profile abnormalities were identified in 29 patients (51.8%), including 13 (56.5%) from the Far North and 16 (48.5%) from the south of the Tyumen region. The lower percentage of endocrine changes in our cohort is likely due to the specific characteristics of the sample.

The high expression of androgen receptors in the myocardium underpins the role of sex hormones in cardiac structural remodeling and their influence on cardiac rhythm through modulation of ion channels. TES, the predominant circulating androgen with numerous genomic and non-genomic (rapid) effects, has a poorly understood and potentially contradictory impact on the cardiovascular system [12]. The oxidative-redox status of the cellular environment has been shown to modulate the cardioprotective or detrimental effects of TES [13].

Table 3.

Dynamics of the results of the 6-minute walk test and EchoCG parameters in the studied groups

Indicator		Group I FN (n=23)	Group II sTr (n=33)	p between groups
6MWT, m	baseline	330.5±85.1	347.6±101.3	0.389
	dynamics	369.2±80.3	383.0±89.1	0.408
p within the group		0.157	0.030	
LA, mm	baseline	50.2±5.0	50.8±5.3	0.481
	dynamics	48.2±11.04	45.6±5.4	0.768
p within the group		0.003	<0.001	
RA, ml	baseline	90.6±34.4	77.0±21.8	0.229
	dynamics	67.9±23.6	68.7±35.6	0.229
p within the group		0.053	0.118	
RV, mm	baseline	31.9±3.9	29.0±4.1	0.016
	dynamics	28.8±3.9	28.2±3.1	0.682
p within the group		0.080	0.088	
LVESD, mm	baseline	59.2±5.3	58.4±7.5	0.575
	dynamics	41.0±9.0	46.0±8.5	0.216
p within the group		0.045	<0.001	
LVEDD, mm	baseline	65.9±6.0	68.9±7.5	0.239
	dynamics	56.0±5.9	60.3±7.9	0.038
p within the group		<0.001	<0.001	
LVESV, ml	baseline	155.7±43.0	172.2±46.4	0.400
	dynamics	79.0±31.6	99.5±40.4	0.091
p within the group		<0.001	<0.001	
LVEDV, ml	baseline	225.7±48.1	250.0±63.3	0.443
	dynamics	156.4±38.6	185.3±57.5	0.042
p within the group		<0.001	<0.001	
IVS, mm		11.0±1.8	10.5±1.5	0.373
LVPW, mm		10.7±1.7	10.5±1.1	0.939
LVEF, %	baseline	31.8±5.3	31.4±4.4	0.956
	dynamics	50.8±8.8	46.4±8.5	0.223
p within the group		<0.001	<0.001	
sPAP, mmHg	baseline	44.4±8.3	42.3±10.3	0.579
	dynamics	27.8±5.7	31.7±9.4	0.123
p within the group		0.020	<0.001	

Note: hereinafter, 6MWT - 6-minute walk test; LA - left atrium; RA - right atrium; RV - right ventricle; LVESD - left ventricular end-systolic diameter; LVEDD - left ventricular end-diastolic diameter; LVESV - left ventricular end-systolic volume; LVEDV - left ventricular end-diastolic volume; IVS - interventricular septum; LVPW - left ventricular posterior wall; LVEF - left ventricular ejection fraction; sPAP - systolic pulmonary artery pressure.

Among its cardioprotective effects, TES exhibits antioxidant properties [14], promotes rapid increases in [Ca2+] i in cardiac myocytes [15], and induces vasodilation [16]. However, TES may also exert pro-oxidant effects [17]. Particularly notable is its adrenomodulatory action, as sympathoadrenal activation is recognized as a key mechanism in the pathogenesis and a mortality factor in CHF. In a rat model of CHF, TES therapy for 4 weeks induced β-2-adrenergic receptor expression, contributing to fibrosis [18]. The observed correlation between TES and norepinephrine (NAdr) in our study suggests a potential association with sympathetic regulation. Increased TES levels in the second group were linked to higher NAdr levels. However, the reduction in myeloperoxidase (MPO) levels in this group may have facilitated greater cardioprotective effects of TES. The absence of changes in TES and MPO in the first group likely indicates strained adaptive mechanisms.

In the second group, a dynamic increase in estradiol (E2) levels was observed, though its role in men remains unclear. Estrogens in men can exert physiological and pathophysiological effects depending on their absolute levels in plasma and cells. The literature discusses the immunomodulatory effects of E2 [19], which align with our findings of its correlation with interleukin-10 (IL-10), a potent anti-inflammatory cytokine that mitigates adverse cardiac remodeling [20].

The biological role of DHEAS remains unclear. During its metabolism, TES and dihydrotestosterone

Table 4.

Dynamics of biomarkers of the sympathoadrenal, immune, neurohumoral systems, and fibroformation in the study groups

Indicator		Reference values	Group I FN (n=23)	Group II sTr (n=33)	p between groups
Adr, ng/ml	baseline	0.018-6.667	2.1[1.2;2.9]	0.6[0.1;2.1]	0.033
	dynamics		0.9[0.3;3.0]	1.5[0.5;2.8]	0.703
p within the group			0.878	0.064	
NAdr, ng/ml	baseline	0.093-33.333	8.0[1.1;21.3]	0.6[0.3;5.6]	0.109
	dynamics		12.4[6.1;21.6]	12.1[3.8;20.2]	0.538
p within the group			0.328	0.028	
NT-proBNP, pg/ml	baseline	<125	1227.0 [764.3;4357.0]	1788.0 [1252.0;3191.0]	0.464
	dynamics		440.0 [249.0;826.0]	602.0 [265.0;1511.0]	0.373
p within the group			0.239	0.003	
IL-6, pg/ml	baseline	0-9.7	3.3[2.2;12.1]	2.5[2.3;3.2]	0.126
	dynamics		2.3[2.0;4.0]	2.3[2.2;3.6]	0.538
p within the group			0.347	0.679	
IL-10, pg/ml	baseline	0-9.1	4.3[2.6;5.0]	2.5[1.7;4.7]	0.194
	dynamics		4.1[3.1;5.0]	3.7[2.2;4.4]	0.074
p within the group			0.697	0.134	
TNF-α, pg/ml	baseline	<8.11	10.2[8.3;11.8]	6.0[4.0;9.3]	0.017
	dynamics		8.0[6.5;10.2]	8.7[7.3;10.5]	0.573
p within the group			0.146	0.043	
CRP, mg/ml	baseline	<3.0	6.9[1.6;11.4]	2.7[1.3;3.7]	0.007
	dynamics		6.8[3.6;11.7]	4.0[2.4;10.3]	0.200
p within the group			0.934	0.062	
MPO, pg/ml	baseline	1.45-72.67	35.3[20.8;76.1]	62.8[27.1;87.8]	0.274
	dynamics		34.9[20.3;76.6]	28.6[19.6;72.1]	0.608
p within the group			0.388	0.049	
MMP-9, ng/ml	baseline	2.0-139.4	172.1 [153.4;255.3]	154.5 [139.4;239.4]	0.551
	dynamics		182.7 [140.4;249.0]	197.5 [154.7;223.7]	0.871
p within the group			0.507	0.910	
TIMP-1, ng/ml	baseline	92-116	428.4 [207.7;628.1]	219.0 [161.1;298.4]	0.043
	dynamics		171.0 [131.0;214.6]	144.3 [111.5;193.0]	0.054
p within the group			0.001	0.002	

Note: hereinafter, Adr - adrenaline; NAdr - noradrenaline; IL - interleukin; TNF-α - tumour necrosis factor alpha; CRP - C-reactive protein; MPO - myeloperoxidase; NT-proBNP - N-terminal pro-brain natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 - tissue inhibitor of matrix metalloproteinase 1.

are synthesized. Low levels of DHEAS have been associated with an increased risk of CHF and mortality [21]. In our study, negative correlations of DHEAS with echocardiographic (Echo) parameters highlight its significant role in cardiac remodeling during CRT. Similarly, the role of progesterone (PGN) in HF remains ambiguous, though it is traditionally considered a precursor hormone for all steroid hormones. A Swedish study in elderly men and women reported an association between PGN and increased HF prevalence [22]. Experimental studies have demonstrated immunosuppressive [23], antimineralocorticoid [24], anti-apoptotic [25], and antiarrhythmic [26] effects of PGN. Additionally, PGN has been shown to enhance myocardial regenerative processes by promoting cardiomyocyte proliferation [27]. In our study, PGN levels decreased dynamically in both groups, correlating with reverse cardiac remodeling under CRT and reduced need for regenerative processes. The identified correlation between PGN and MMP-9 indicates its influence on extracellular cardiac matrix remodeling.

In the first group, the higher prevalence of AF requiring RFA of the AVJ likely indicates more pronounced cardiac remodeling. Literature data on the association of sex hormones with AF remain contradictory. A meta-analysis by P. Hu et al. (2022), encompassing 3,979 studies, suggested that higher endogenous DHEAS levels are associated with a lower risk of AF in men, whereas no relationship was found between TES, estradiol (E2) concentrations, and AF risk [28]. The initially low DHEAS level in conjunction with other factors in the first group may have contributed to the onset of AF.

Table 5.

Dynamics of hormones in the study groups

Indicator		Reference values	Group I FN (n=23)	Group II sTr (n=33)	p between groups
TES, nmol/L	baseline	7.35-25.7	17.0 [12.5;19.9]	15.0 [11.1;19.2]	0.443
	dynamics		16.6 [13.0;24.9]	17.3 [12.8;23.3]	0.807
p within the group			0.875	0.019	
E2, ng/mL	baseline	0-56.0	44.3 [31.2;58.0]	34.4 [22.9;42.3]	0.210
	dynamics		51.4 [28.3;106.0]	47.8 [28.7;53.8]	0.202
p within the group			0.300	0.048	
PGN, nmol/L	baseline	0-2.39	2.0 [1.2;2.3]	1.2 [0.8;2.3]	0.223
	dynamics		0.7 [0.6;1.0]	0.8 [0.6;1.2]	0.274
p within the group			0.004	0.036	
DHEAS, µg/dL	baseline	80.0-560	67.1 [15.0;132.3]	67.7 [47.2;158.3]	0.528
	dynamics		83.9 [56.8;124.5]	130.5 [51.1;181.0]	0.256
p within the group			0.308	0.209	
CORT, nmol/L	baseline	138-690	505.0 [423.8;563.5]	341.0 [295.5;456.8]	0.014
	dynamics		425.0 [273.5;561.5]	306.5 [183.8;527.5]	0.558
p within the group			0.343	0.582	
PTH, pg/mL	baseline	11.0-67.0	81.6 [48.8;117.5]	59.3 [34.1;101.0]	0.274
	dynamics		57.7 [39.4;77.3]	72.6 [56.1;88.4]	0.053
p within the group			0.094	0.936	
TTH, ME/ml	baseline	0.4-4.0	2.7 [2.0;4.0]	2.0 [1.3;2.8]	0.049
	dynamics		1.8 [1.3;2.2]	1.6 [1.1;2.7]	0.981
p within the group			0.126	0.345	
fT3, pg/mL	baseline	1.5-4.1	3.1 [2.7;3.4]	3.5 [2.9;3.8]	0.333
	dynamics		3.2 [2.7;3.9]	2.7 [2.5;3.9]	0.565
p within the group			0.337	0.633	
fT4, pmol/l	baseline	10.3-24.5	18.5 [15.8;20.7]	15.9 [13.6;17.2]	0.023
	dynamics		14.9 [11.8;17.2]	15.6 [13.3;18.2]	0.509
p within the group			0.235	0.960	
cT3/cT4, units	baseline		0.115 [0.089;0.147]	0.142 [0.118;0.170]	0.045
	dynamics		0.128 [0.110;0.210]	0.120 [0.086;0.171]	0.389
p within the group			0.302	0.715	

Note: hereinafter, TES - total testosterone; E2 - estradiol; PGN - progesterone; DHEAS - dehydroepiandrosterone sulfate; CORT - cortisol; PTH - parathyroid hormone; fT3 - free triiodothyronine; fT4 - free thyroxine.

Thyroid dysfunction is a common comorbidity in CHF. According to K.W. Streng et al. (2018), thyroid dysfunction was identified in 10.9% of patients with reduced LVEF, 13.7% of those with mid-range LVEF, and 17.9% with preserved LVEF [29]. The low prevalence of thyroid pathology in our study is likely due to the specificity of the cohort, which included only CRT responders with preserved adaptive capacity. TH effects on the heart include genomic mechanisms promoting cardiac differentiation during the perinatal period and nongenomic actions maintaining cardiovascular homeostasis [30]. Free triiodothyronine (fT3) plays a central role in regulating metabolic activity and exerts negative feedback on the pituitary gland. It influences cardiac genes encoding contractile proteins, the α- and β-myosin heavy chains, sodium-calcium exchange, and sarcoplasmic reticulum calcium ATPase (SERCA2), and affects β-adrenergic receptors. By acting on these mechanisms, T3 increases myocardial contractility, reduces vascular resistance by dilating peripheral arterioles, regulates mitochondrial function and morphology, and mediates antifibrotic and proangiogenic effects, promoting regeneration and recovery processes [31].

In CHF, T4-to-T3 conversion in cardiac muscle decreases due to hypoxia, immune inflammation activation, oxidative stress, and glutathione peroxidase deficiency, reducing deiodinase activity in the ventricular myocardium. This, combined with reduced T3 plasma levels, may decrease intracellular T3 bioavailability [32]. A reduction in serum T3 without an increase in TSH levels is termed "Low-T3 syndrome," which affects 30% of CHF patients [33]. Even minor alterations in circulating TH concentrations within the normal range are associated with increased cardiovascular risk [34]. Both fT4 and the fT3/fT4 ratio are independent predictors of cardiovascular mortality [35], and a low fT3/fT4 ratio predicts all-cause mortality in HF patients [36].

Subclinical hypothyroidism has been linked to the ineffectiveness of CRT [37]. Low fT3 levels correlate with worsened cardiac function and an unfavourable prognosis following CRT implantation [38]. In our study, hypothyroidism was identified in 3 (13.0%) northerners, and subclinical hyperthyroidism in 1 (4.3%). Low fT3 levels were observed in 6 (26.1%) men in Group 1 and 4 (12.1%) in Group 2. Initially, higher mean TSH and fT4 levels, along with a lower fT3/fT4 ratio, were documented in Group 1. Deviations in TH levels, even within the normal reference range, can significantly impact health. Elevated fT4 levels in Group 1 likely reflect impaired conversion to fT3 due to hypoxia in FN conditions. Positive correlations of TSH with TNF-α and echocardiographic parameters, alongside a negative association with LVEF, underscore TSH's critical role in cardiac homeostasis and reverse remodeling processes in CRT patients.

Cortisol (CORT), the primary glucocorticoid hormone produced in the adrenal gland's zona fasciculata, is often termed the "stress hormone." It regulates diverse physiological functions, including energy metabolism, electrolyte balance, blood pressure, and cognitive functions. Stress triggers the release of GCs, such as CORT, and catecholamines, like adrenaline (Adr). In our study, significantly elevated CORT levels in Group 1 correlated with higher Adr levels compared to Group 2, indicating chronic stress and strained adaptive capacity among northern-

Table 6.

Correlations of hormone levels with echocardiography parameters and biomarkers

	PTH	TEC	PGN	DHEAS	E2	TSH	CORT
TSH	r=0.442 p=0.031						
fT4					r=-0.568 p=0.006		
PTH						r=0.442 p=0.031	
N T - proBNP	r=0.266 p=0.062						
MMP-9			r=0.320 p=0.021				r=0.665 p=0.026
NAdr		r=0.347 p=0.023					
IL-10					r=0.367 p=0.006		
TNF-α						r=0.352 p=0.072	
LA				r=-0.312 p=0.021		r=0.389 p=0.045	
RA	r=0.328 p=0.026			r=-0.397 p=0.004			
RV	r=0.304 p=0.033			r=-0.323 p=0.018			
LVEDD						r=0.348 p=0.076	
LVESD	r=0.427 p=0.015						
LVESV						r=0.340 p=0.082	
LVEF						r=-0.340 p=0.083	
SPAP	r=0.327 p=0.064			r=-0.334 p=0.046			

ers. GC signalling occurs via glucocorticoid receptors in cardiomyocytes, essential for maintaining normal cardiac morphology and function. However, GCs may also bind mineralocorticoid receptors, which are highly expressed in the myocardium of HF patients. Activation of these receptors can disrupt calcium, magnesium, and other ion regulation, induce mitochondrial calcium overload, and promote oxidative stress and immune inflammation, resulting in subsequent remodeling, interstitial fibrosis, and CHF [39].

In our study, the initially higher CORT levels in northerners were associated with heightened immune activation and fibrogenesis imbalance. Myeloperoxidase (MPO) levels, a marker of oxidative stress activity, were within the reference range across all study points in both groups. However, Group 2 demonstrated a significant reduction in MPO levels over time, whereas no dynamic changes were observed in Group 1 under chronic stress conditions. Moderate correlations between CORT and MMP-9 suggest its role in modulating the extracellular cardiac matrix. Associations of higher CORT levels with elevated Adr, cytokines, and CRP levels further support the concept of chronic stress and strained adaptive mechanisms in northerners.

PTH (parathyroid hormone) impacts cardiomyocyte physiology by activating G-protein signalling and subsequent calcium influx into cardiac cells, which does not directly induce contractility but causes several indirect effects on the myocardium. PTH promotes protein kinase C activation, potentially weakening contractility by inhibiting β-adrenergic receptor stimulation. Hypercalcaemia increases catecholamine (Adr and NAdr) release and arterial response to catecholamines [40]. Correlations between PTH levels and CHF severity have been reported [41], although its prognostic role remains controversial. PTH serves as a reliable biomarker of congestion in HF patients, associated with peripheral oedema and orthopnoea [42]. Literature also highlights a link between PTH levels and AF incidence [43].

In our study, baseline PTH levels in Group 1 exceeded reference values and were associated with higher initial Adr levels and arrhythmias in the form of tachycardic AF requiring RFA AVJ. Elevated PTH levels were observed in 18 (32.1%) patients, including 9 (39%) northerners and 9 (27.3%) patients from the sTr. Correlations between PTH and echocardiographic parameters, as well as NT-proBNP levels, support its involvement in cardiac remodeling and HF severity verification. It has been demonstrated that PTH adds prognostic value to NT-proBNP and serves as an independent predictor of cardiovascular events [44].

The greater severity of HF in Group 1 was further verified by elevated baseline levels of TIMP-1, TNF-α, CRP, Adr, and increased right ventricular dimensions. Fibrosis and inflammation are interlinked mechanisms driving HF progression [45]. The observed association of 5-year survival in northerners with IL-6 levels indicates the independent impact of immune inflammation on prognosis. The literature discusses the prognostic significance of the right ventricle [46]. Long-term (lifetime) hypoxia triggers adaptive responses, including sympathetic activation and hypoxic pulmonary vasoconstriction [47], which increases right heart strain, reduces right ventricular output, and eventually leads to its enlargement. This highlights the heart's ability to adapt successfully to hypoxia both in the short and long term.

Comparable 5-year survival rates across the groups may be attributed to the numerous effects of CRT, including immunosuppressive and adrenomodulating influences [48], effects on thyroid function [49], sex steroids [50], oxidative stress [51], and fibrosis [52].

Study limitations

The limitations of our study include its single-centre design and the inclusion of a small number of patients.

CONCLUSION

Thus, male CRT responders residing in the Far North exhibited a complex set of adaptive reactions, including elevated levels of cortisol and thyroid hormones (TSH, fT4), reduced fT3/fT4 ratio, increased parathyroid hormone levels, associated with heightened sympatho-adrenal and immune activation, fibroformation imbalance, larger right ventricular dimensions, and a higher incidence of tachysystolic atrial fibrillation requiring AVJ RFA. These findings likely reflect the complex pathophysiological nature of the Arctic strain syndrome, which contributes to the development of heart failure in Arctic conditions. Comparable 5-year survival rates between Far North residents and patients from the southern Tyumen region were attributed to the modulatory effects of CRT. The observed association of survival in Far North patients with IL-6 levels highlights the independent impact of immune inflammation on prognosis.

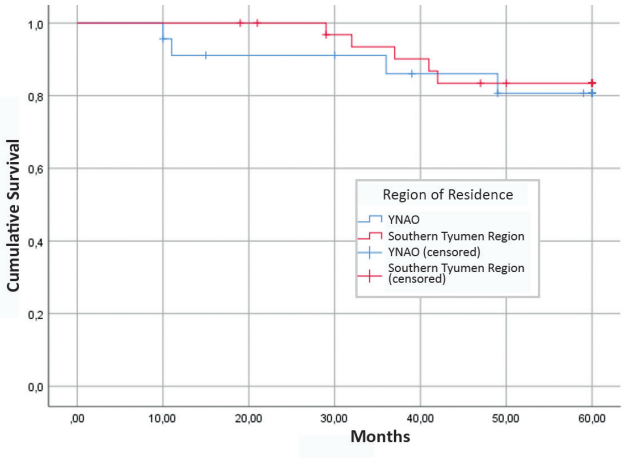

Fig. 1. Five-year survival of male responders to cardiac resynchronization therapy under the age of 65.

Table 7.

Results of Cox multivariate regression analysis

	Factors	HR (95% CI)	p
Group I - FN (n=23)	IL-6	4.013 (1.278-12.605)	0.017
	TIMP-1	0.986 (0.959-1.012)	0.290
	NT-proBNP	1.000 (1.000-1.001)	0.489
Group II - sTr (n=33)	LVEDV	1.032 (0.979-1.088)	0.237
	LVESV	0.969 (0.899-1.044)	0.408
	LVEF	0.887 (0.698-1.127)	0.327
	MMP-9	0.991 (0.964-1.020)	0.543

Note: hereinafter, HR - Hazard Ratio; CI - Confidence Interval.

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *European Journal of Heart Failure*. 2020;22(8): 1342-56. https://doi.org/10.1002/ejhf.1858.
2. Polyakov DS, Fomin IV, Belenkov YuN, et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of follow-up? Results of the EPOCH-CHF study. *Kardiologiia*. 2021;61(4): 4-14 (In Russ.). https://doi.org/10.18087/cardio.2021.4.n1628.
3. Xanthopoulos A, Skoularigis J, Triposkiadis F. The Neurohormonal Overactivity Syndrome in Heart Failure. *Life (Basel)*. 2023 Jan; 13(1): 250. https://doi.org/10.3390/life13010250.
4. Gronda E, Dusi V, D'Elia E, et al. Sympathetic activation in heart failure. *European Heart Journal Supplements*. 2022 September; 24(Supplement_E): E4-E11. https://doi.org/10.1093/eurheartjsupp/suac030.
5. Castillo EC, Vázquez-Garza E, Yee-Trejo D, et al. What Is the Role of the Inflammation in the Pathogenesis of Heart Failure? *Curr Cardiol Rep*. 2020 Sep 10;22(11): 139. https://doi.org/10.1007/s11886-020-01382-2.
6. Nikolov A, Popovski N. Extracellular Matrix in Heart Disease: Focus on Circulating Collagen Type I and III Derived Peptides as Biomarkers of Myocardial Fibrosis and Their Potential in the Prognosis of Heart Failure: A Concise Review. *Metabolites*. 2022 Mar 28;12(4): 297. https://doi.org/10.3390/metabo12040297.
7. Korchin VI, Korchina TYa, Ternikova EM, et al. Influence of Climatic and Geographical Factors of the Yamalo-Nenets Autonomous Okrug on the Health of Its Population (Review). *Journal of Medical and Biological Research*. 2021;9(1): 77-88. (In Russ.). https://doi.org/10.37482/2687-1491-Z046.
8. Vetoshkin AS, Shurkevich NP, Gapon LI, et al. Carotid atherosclerosis, arterial hypertension, and left ventricular remodeling in men working on a rotational basis in the Far North. *The Siberian medical Journal*. 2020;35(1): 159-66. (In Russ.). https://doi.org/10.29001/2073-8552-2020-35-1-159-166.
9. Dronov AV, Sitnikiva My, Grineva EN, Shlyahto EV, Solncev VN. Dynamics of growth hormone content and insulin-like growth factor-1 in the blood patients with decompensated chronic heart failure as a marker of prognosis and effectiveness of therapy. Journal Heart Failure. 2013. V14;6(80):329-333 (In Russ). ISSN 1728-4651.
10. Mancini A, Fuvuzzi AMR, Bruno C, et al. Anabolic Hormone Deficiencies in Heart Failure with Reduced or Preserved Ejection Fraction and Correlation with Plasma Total Antioxidant Capacity. *Int J Endocrinol*. 2020; 2020: 5798146. https://doi.org/10.1155/2020/5798146.
11. Cittadini A, Salzano A, Iacoviello M, et al. Multiple hormonal and metabolic deficiency syndrome predicts outcome in heart failure: the T.O.S.CA. Registry. *Eur J Prev Cardiol*. 2021 Dec 29;28(15): 1691-700. https://doi.org/10.1093/eurjpc/zwab020.
12. Diaconu R, Donoiu I, Mirea O, et al. Testosterone, cardiomyopathies, and heart failure: a narrative review. *Asian J Andro*l. 2021 Jul-Aug; 23(4): 348-56. https://doi.org/10.4103/aja.aja_80_20.
13. Cruz-Topete D, Dominic P, Stokes KY. Uncovering sex-specific mechanisms of action of testosterone and redox balance. *Redox Biol.* 2020 Apr;31: 101490. https://doi.org/10.1016/j.redox.2020.101490.
14. Zhang L, Wu S, Ruan Y, et al. Testosterone suppresses oxidative stress via androgen receptor-independent pathway in murine cardiomyocytes. *Mol. Med. Rep.* 2011;4: 1183-88. https://doi.org/10.3892/mmr.2011.539.
15. Foradori CD, Weiser MJ, Handa RJ. Non-genomic actions of androgens. *Front Neuroendocrinol.* 2008 May;29(2): 169-81. https://doi.org/10.1016/j.yfrne.2007.10.005.
16. Lorigo M, Melissa MM, Lemos MC, et al. Vascular mechanisms of testosterone: The non-genomic point of view. *The Journal of Steroid Biochemistry and Molecular Biology.* 2020;196: 105496. https://doi.org/10.1016/j.jsbmb.2019.105496.
17. Pingili AK, Kara M, Khan NS, et al. 6beta-hydroxytestosterone, a cytochrome P450 1B1 metabolite of testosterone, contributes to angiotensin II-induced hypertension and its pathogenesis in male mice. *Hypertension.* 2015;65: 1279-87. https://doi.org/10.1161/HYPERTENSIONAHA.115.05396.
18. Sun J, Fu L, Tang X et al. Testosterone Modulation of Cardiac β-Adrenergic Signals in a Rat Model of Heart Failure. *Gen Comp Endocrinol.* 2011 Jul 1;172(3): 518-25. https://doi.org/10.1016/j.ygcen.2011.04.019.
19. Xing D, Oparil YuH, Gong K, et al. Estrogen modulates NFkB signaling by enhancing Ikβα levels and blocking p65 binding at the propmotors of inflammatory genes via estrogen receptor-β. *PLoS ONE*. 2012;7: e36890. https://doi.org/10.1371/journal.pone.0036890.
20. Stafford N, Assrafally F, Prehar S, et al. Signaling via the Interleukin-10 Receptor Attenuates Cardiac Hypertrophy in Mice During Pressure Overload, but not Isoproterenol Infusion. *Front Pharmaco*l. 2020; 11: 559220. https://doi.org/10.3389/fphar.2020.559220.
21. Jia X, Sun C, Tang O, et al. Plasma Dehydroepiandrosterone Sulfate and Cardiovascular Disease Risk in Older Men and Women. *J Clin Endocrinol Metab.* 2020 Dec; 105(12): e4304-27. https://doi.org/10.1210/clinem/dgaa518.
22. Nilsson SE, Fransson E, Brismar K. Relationship Between Serum Progesterone Concentration and Cardiovascular Disease, Diabetes, and Mortality in Elderly Swedish Men and Women: An 8-Year Prospective Study. *Gender Medicine*. 2009;6(3): 433-43. https://doi.org/10.1016/j.genm.2009.09.011.
23. Lei B, Mace B, Dawson HN et al. Anti-Inflammatory Effects of Progesterone in Lipopolysaccharide-Stimulated BV-2 Microglia. *PLoS One*. 2014;9(7): e103969. https://doi.org/10.1371/journal.pone.0103969.
24. Quinkler M, Meyer B, Bumke-Vogt C, et al. Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. *European Journal of Endocrinology*. 2002; 146:789-800. https://doi.org/10.1530/eje.0.1460789.
25. Morrissy S, Xu B, Aguilar D, et al. Inhibition of apoptosis by progesterone in cardiomyocytes. *Aging Cell.*2010;9: 799-809. https://doi.org/10.1111/j.1474-9726.2010.00619.x.

26. Ma J, Hong K, Wang HS. Progesterone protects against bisphenol A-induced arrhythmias in female rat cardiac myocytes via rapid signaling. *Endocrinology.* 2017;158: 778-90. https://doi.org/10.1210 / en.2016-1702.
27. Lan C, Cao N, Chen C, et al. Progesterone, via yes-associated protein, promotes cardiomyocyte proliferation and cardiac repair. *Cell Prolif.* 2020;53(11): e12910. https://doi.org/10.1111 / cpr.12910.
28. Hu P, Huang J, Lu Y, et al. Circulating sex hormones and risk of atrial fibrillation: A systematic review and meta-analysis. *Front Cardiovasc Med.* 2022;9: 952430. https://doi.org/10.3389/fcvm.2022.952430.
29. Streng KW, Nauta JF, Hillege HL et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. *International Journal of Cardiology*. 2018;271: 132-9. http://creativecommons.org/licenses/by-nc-nd/4.0.
30. Mastorci F, Sabatino L, Vassalle C, et al. Cardioprotection and Thyroid Hormones in the Clinical Setting of Heart Failure. *Front Endocrinol (Lausanne).* 2020 Jan 28;10: 927. https://doi.org/10.3389/fendo.2019.00927.
31. Mantzouratou P, Malaxianaki E, Cerullo D, et al. Thyroid Hormone and Heart Failure: Charting Known Pathways for Cardiac Repair / Regeneration. *Biomedicines.* 2023;11: 975. https://doi.org/10.3390/ biomedicines11030975.
32. Troshina EA, Senyushkina ES. Metabolic Systemic Effects Triiodothyronine. *The Russian Archives of Internal Medicine.* 2020; 10(4): 262-71. (In Russ.). https://doi.org/10.20514/2226-6704-2020-10-4-262-271.
33. Iervasi G, Pingitore A, Landi P, et al. Low-T3 syndrome. A strong prognostic predictor of death in patients with heart disease. *Circulation.* 2003;107(5): 708-13. https://doi.org/10.1161/01.cir.0000048124.64204.3f.
34. Taylor PN, Razvi S, Pearce SH, et al. Clinical review: a review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab*. 2013;98(9): 3562-71. https://doi.org/10.1210/jc.2013-1315.
35. Lang X, Li Y, Zhang D, et al. FT3/FT4 ratio is correlated with all-cause mortality, cardiovascular mortality, and cardiovascular disease risk: NHANES 2007-2012. *Front Endocrinol (Lausanne).* 2022 Aug;18;13: 964822. https://doi.org/10.3389/fendo.2022.964822.
36. Wang C, Han S, Li Y, et al. Value of FT3/FT4 Ratio in Prognosis of Patients With Heart Failure: A Propensity-Matched Study. *Front Cardiovasc Med*. 2022 Apr 12;9: 859608. https://doi.org/10.3389/fcvm.2022.859608.
37. Balli M, Köksal F, Söylemez N, et al. Subclinical hypothyroidism and its relationship with therapy failure in patients underwent cardiac resynchronization therapy. *Eur Rev Med Pharmacol Sci*. 2022 Dec;26(23): 8719-27. https://doi.org/10.26355/eurrev_202212_30544.
38. Chen Y-Y, ShuX-R, Su Z-Z, et al. A Low-Normal Free Triiodothyronine Level Is Associated with Adverse Prognosis in Euthyroid Patients with Heart Failure Receiving Cardiac Resynchronization Therapy. *Int Heart J.* 2017 Dec 12;58(6): 908-14. https://doi.org/10.1536/ihj.16-477.
39. Kim J, Yun K-S, Cho A, et al. High cortisol levels are associated with oxidative stress and mortality in maintenance hemodialysis patients. *BMC Nephrol*. 2022 Mar 8;23(1): 98. https://doi.org/10.1186/s12882-022-02722-w.
40. Vlachakis ND, Frederics R, Valasquez M, et al. Sympathetic system function and vascular reactivity in hypercalcemic patients. *Hypertension*. 1982. May-Jun; 43: 452-8. https://doi.org/10.1161/01.hyp.4.3.452.
41. Altay H, Zorlu A, Binici S, et al. Relation of serum parathyroid hormone level to severity of heart failure. *Am J Cardiol*. 2012;109(2): 252-56. https://doi.org/10.1016/j.amjcard.2011.08.039.
42. Scicchitano P, Iacoviello M, Passantino A, et al. Plasma Levels of Intact Parathyroid Hormone and Congestion Burden in Heart Failure: Clinical Correlations and Prognostic Role. *J Cardiovasc Dev Dis.* 2022;9(10): 334. https://doi.org/10.3390/jcdd9100334.
43. Kerkutluoglu M, Yucel O, Gunes H, et al. The Relationship Between Atrial Fibrillation and Parathyroid Hormone in Heart Failure Outpatients. *Kardiologiia.* 2023;63(9): 51-5. https://doi.org/10.18087/cardio.2023.9.n2277.
44. Gutiérrez-Landaluce C, AceñaA, Pello A, et al. Parathormone levels add prognostic ability to N-terminal pro-brain natriuretic peptide in stable coronary patients. *ESC Heart Fail*. 2021 Aug;8(4): 2713-22. https://doi.org/10.1002/ehf2.13331.
45. Rao M, Wang X, Guo G, et al. Resolving the intertwining of inflammation and fibrosis in human heart failure at single-cell level**.** *Basic Res Cardiol*. 2021 Oct 3;116(1): 55. https://doi.org/10.1007/s00395-021-00897-1.
46. Galloo X, Stassen J, Hirasawa K, et al. Prognostic Implications of Right Ventricular Size and Function in Patients Undergoing Cardiac Resynchronization Therapy. *Circulation: Arrhythmia and Electrophysiology*. 2023;16(2). https://doi.org/10.1161/CIRCEP.122.011676.
47. Williams AM, Levine BD, Stembridge M. A change of heart: Mechanisms of cardiac adaptation to acute and chronic hypoxia. J Physiol. 2022 Sep;600(18):4089-4104. doi: 10.1113/JP281724.
48. Kuznetsov VA, Enina TN, Gorbatenko EA, et al. Five-year survival and biomarkers of sympatho-adrenal, neurohumoral, immune activation, fibrosis in patients with early and late superresponse to cardiac resynchronization therapy. *Journal of Arrhythmology*. 2021;28(2): 18-27. (In Russ.). https://doi.org/10.35336/VA-2021-2-18-27.
49. Celikyurt U, Agacdiken A, Geyik B, et al. Effect of Cardiac Resynchronization Therapy on Thyroid Function. *Clin Cardiol*. 2011 Nov; 34(11): 703-5. https://doi.org/10.1002/clc.20952.
50. Enina TN, Shirokov NE, Petelina TI. Association of sex hormone dynamics with 10-year survival in men with implanted cardiac resynchronization therapy devices. *Journal of Arrhythmology*. 2022;29(2): 5-16. (In Russ.). https://doi.org/10.35336/VA-2022-2-01. https://elibrary.ru/aekjxb.
51. Sultan A, Wörmann J, Lüker J, et al. Significance of myeloperoxidase plasma levels as a predictor for cardiac resynchronization therapy response. *Clin Res Cardiol*. 2021 Aug;110(8): 1173-80. https://doi.org/10.1007/s00392-020-01690-1.
52. McAloon CJ, Barwari T, Hu J et al. Characterisation of circulating biomarkers before and after cardiac resynchronisation therapy and their role in predicting CRT response: the COVERT-HF study. *Open Heart*. 2018 Oct 18;5(2): e000899. https://doi.org/10.1136/openhrt-2018-000899.

https://doi.org/10.35336/VA-1355

NONFLUOROSCOPIC CATHETER ABLATION OF TACHYARRHYTHMIAS IN PATIENTS WITH ANTIARRHYTHMIC DEVICES

E.B.Kropotkin, E.A. Ivanitskiy, T.A.Gorton, V.A.Sakovich
Federal Center of Cardiovascular Surgery, Russia, Krasnoyarsk, 45 Karaulnaya str.

Aim. To assess safety and effectiveness of zero fluoro catheter ablation (CA) of tachyarrhythmias in patients with antiarrhythmic device.

Methods. One hundred ninety-seven patients with implanted antiarrhythmic device and indication for catheter ablation of tachyarrhythmias were included in retrospective study. In control group of patients n=63 (mean age 65.5±11.9 years) all procedures were performed under fluoroscopic guidance. In a study group, n=134 (mean age 66.1±15.6 years) all procedures were performed without the use of fluoroscopy. To reconstruct 3D anatomy we used navigation systems: magnet and impedance. In some cases we used intracardiac ultrasound. In the first group there were 65% of patients with pacemakers, 4.8% patients with implantable cardioverters-defibrillators and 30.2% of patients had cardiac resynchronization systems. In second 70.1%, 12.7% and 17.2% respectively. In control group CA was performed within 24 hours after device implantation in 13 patients (20.6%), in study group - 23 (17.2%). In the rest cohort of patients mean period between device implantation and CA was 29.26±28 months - in control group, 38.8±39 months. Antiarrhythmic device programming was performed before and right after CA.

Results. Interventional catheter procedure was performed in 98.4% of patients in control group and in 98.5% of patients in study group. Radiation exposure in control group was 0.24 mZv, in study group 0 mZv. There were no conversions from zero fluoroscopy procedure to X -ray controlled due to different reasons. In control (fluoroscopy controlled) group 8 hours after CA ventricle lead dislodgement was diagnosed. Antiarrhythmic device in this patient was implanted 6 days before CA. There were no lead dislodgements or cardiac pacing disorders in study group.

Conclusion. Zero fluoroscopy CA of tachyarrhythmias in patients with antiarrhythmc device is as safe and effective as standard fluoroscopy controlled procedure.

Key words: fluoroscopy; zero fluoroscopy; catheter ablation; implantable antiarrhythmic device; atrial fibrillation; atrial flutter; ventricular arrhythmias

Conflict of Interests: none.
Funding:none.
Received: 14.03.2024 **Revision Received:** 05.08.2024 **Accepted:** 06.10.2024
Corresponding author: Evgeny Kropotkin, E-mail: kroj@inbox.ru

E.B.Kropotkin - ORCID ID 0000-0001-9094-378X, E.A. Ivanitskiy - ORCID ID 0000-0002-4946-8005,V.A.Sakovich - ORCID ID 0000-0001-7743-8770

For citation: Kropotkin EB, Ivanitskiy EA, Gorton TA, Sakovich VA. Zero fluoroscopy catheter ablation in patients with implanted antiarrhythmic devices. *Journal of Arrhythmology.* 2024;31(4): 17-23. https://doi.org/10.35336/VA-1355.

Currently, radiofrequency catheter ablation (RFA) is the treatment of choice for various types of tachyarrhythmias [1–3]. However, performing such procedures typically requires the use of fluoroscopy to visually guide manipulations within the heart and major vessels [4]. Fluoroscopy, in turn, is a source of ionizing radiation, which negatively affects both the patient and the medical staff"[5, 6]. The active use of 3D navigation systems for such procedures reduces the need for fluoroscopy[7]. In some cases, interventions can be performed with minimal radiation exposure[8, 9] or even without its use at all [10, 11].

The use of 3D navigation systems allows for the reconstruction of the heart chambers on one hand, and visualization of electrophysiological catheters used for RFA on the other. However, these systems cannot visualize endocardial leads (ELs) of cardiac implanted electronic devices (CIED) or heart valves. As a result, performing RFA in patients with implanted CIED carries certain risks to the ELs, such as damage, lead dislodgement, increased pacing thresholds, and more. According to our knowledge, performing RFA without any fluoroscopy in patients with CIED has not been described in the global literature to date.

In this study, we retrospectively analyzed the experience of performing non-fluoroscopic RFA in patients with implanted CIED.

METHODS

From January 1, 2016, to January 30, 2021, 197 patients with CIED underwent RFA for tachyarrhythmias. Standard procedures using fluoroscopy (control group) were performed on 63 patients, while alternative non-fluoroscopic procedures (study group) were performed on 134 patients. The clinical characteristics of patients in both groups are presented in Table 1.

Indications for surgery were determined based on the recommendations of the Russian Society of

Arrhythmologists (RSO) and following mandatory CIED programming. Procedures in both groups were performed in a fluoroscopy-equipped operating room. In the control group, fluoroscopy was routinely used for catheter visualization, while in the study group, magnetic and impedance-based navigation systems were utilized. Surface ECG registration and endocardial electrophysiological studies, including endogram recordings, were performed uniformly in both groups. Intracardiac ultrasound was used for transseptal punctures.

In cases of atrioventricular nodal reentrant tachycardia (AVNRT), which occurred only in the study group, non-irrigated ablation catheters were used in 7 patients (5.2%), while irrigated catheters were used in all other cases. For patients with implanted cardioverter-defibrillators (ICDs), the high-energy shock function was disabled in the operating room prior to the procedure. Immediately after the procedure, pacing parameters for each lead were checked, and the shock function was reactivated.

During atrioventricular node ablation (AVNA), dual- or triple-chamber CIED were programmed to the VVI mode with a basal heart rate (HR) of 30 beats per minute. For single-chamber CIED (implanted only in patients with permanent atrial fibrillation (AF)), the basal HR was programmed to 30 bpm. Following the creation of a third-degree atrioventricular block, dual- and triple-chamber CIED were returned to atrioventricular pacing mode with physiological basal HR values programmed. In single-chamber CIED, the previous basal HR settings were restored.

In the control group, RFA was performed simultaneously with CIED implantation or within the first 24 hours after implantation in 13 patients (20.6%), and in the study group, in 23 patients (17.2%). In other cases, the period between CIED implantation and RFA for tachyarrhythmias was 29.26 ± 28 months (range 1–111 months) in the control group and 38.8 ± 39 months (range 1–201 months) in the study group. The types and scope of procedures in both groups are presented in Table 2.

On the day following the procedure, all patients underwent device reprogramming by the operating surgeon or attending cardiologist. For patients with chronically implanted pacemakers (>1 year), follow-ups occurred once every 12 months, and for those with ICDs, every 6 months. If CIED implantation and RFA were performed during the same hospitalization, device reprogramming was scheduled 6 months after discharge, regardless of the device type.

Mandatory tests on the day following RFA included echocardiography and ultrasound examination of femoral puncture sites in the major vessels. Chest X-rays were included in the postoperative examination protocol for patients who had undergone RFA via subclavian access or in cases of changes in stimulation parameters of endocardial CIED leads during programming.

RESULTS

Interventional catheter procedures were performed in 98.4% of patients in the control group and 98.5% of patients in the study group. In one case in the control group, RFA of a ventricular ectopic focus in the right ventricular outflow tract (RVOT) was unsuccessful due to its proximity to the site of the endocardial ventricular lead implantation. In all other cases, RFA was successfully performed.

In the study group, RFA was unsuccessful in two patients with ventricular ectopic foci. In the first case, the ectopic focus in the left ventricular outflow tract could not be accessed due to the presence of an aortic valve prosthesis, and transseptal access was not considered by the operating surgeon. In the second case, attempts at RFA were not made due to the ectopic activity's proximity to the cardiac conduction system and the high risk of developing atrioventricular block in a patient with a single-chamber ICD. Both patients were prescribed antiarrhythmic drug therapy with positive results. In all other cases, RFA was successfully performed.

Radiation exposure during RFA was 0 mSv in the study group and 0.24 ± 0.5 mSv in the control group (range 0.001–2.625 mSv). The radiation dose reflects the RFA procedure only, excluding preoperative or postoperative imaging. The study aimed to assess the feasibility of fully

Table 1.

Clinical characteristics of patients included in the study

Indicator	Study group	Control group
Gender (male/female)	55/79	31/32
Age, years	66.1±15.6	65.5±11.9
Height, cm	165.2±9.8	165.7±9.33
Weight, kg	79.2± 17.6	87.4±16.6
Impaired glucose tolerance, n (%)	29 (21.6)	15 (23.8)
Hypertension, n (%)	106 (79.1)	55 (87.3)
Chronic kidney disease, n (%)	32 (23.9)	4 (6.3)
Obesity, n (%)	35 (26.1)	20 (31.7)
Thyroid dysfunction, n (%)	34 (25.4)	12 (19)
Cerebrovascular accident, n (%)	10 (7.5)	11 (17.5)
Oncological history, n (%)	16 (11.9)	7 (11.1)
Stenting*, n (%)	19 (14.2)	16 (25.4)
Open-heart surgery, n (%)	18 (13.4)	3 (4.8)
Implanted PM, n (%)	94 (70.1)	41 (65)
Implanted ICD, n (%)	17 (12.7)	3 (4.8)
Implanted CRT-P / CRT-D, n (%)	23 (17.2)	19 (30.2)

Note: Hereinafter, * - Coronary and major arteries; P - Pacemaker; ICD - Implantable cardioverter-defibrillator; CRT - Cardiac resynchronization therapy.

non-fluoroscopic RFA. The preoperative preparation and postoperative protocols were identical in both groups, but the total radiation dose for hospitalization was documented in the discharge summary.

In this study, no conversions from non-fluoroscopic to fluoroscopy-controlled procedures were required. Intracardiac ultrasound was additionally used in one patient with an ICD and recurrent ventricular tachycardia originating from the left ventricle after unsuccessful retrograde transaortic catheter ablation attempts. Using transseptal access, the ablation catheter was guided into the left ventricle through the mitral valve with a steerable introducer. The operative times for each condition are shown in Table 3.

In the control group, a patient underwent RFA of the AVN for drug-resistant AF/flutter six days after pacemaker implantation. The patient had a history of RFA for AF/flutter five years prior. Eight hours post-RFA, the patient's condition deteriorated due to ventricular lead dislodgement and third-degree AV block, with a heart rate of 36 bpm. Following ventricular lead reimplantation, the patient's condition stabilized. In all other cases, no dysfunction of the CIED was detected during early postoperative programming in either group.

In the control group, one case of restored AV node conduction after RFA required repeat ablation during the same hospitalization. In the study group, a patient with atypical left atrial flutter (AFL) after mitral valve replacement experienced flutter recurrence during pacemaker programming the next day. Repeat intervention was not performed during the same hospitalization. The pacemaker was set to DDIR mode with a basal HR of 70 bpm, and antiarrhythmic therapy was prescribed.

External cardioversion to restore sinus rhythm was performed in two patients (3.2%) in the control group after RFA for AF and nine patients (6.7%) in the study group. Three cases followed ablation for AF, and three followed ablation for typical atrial flutter, where two patients presented with AF at the procedure's start, and one developed AF during ablation. Two cases occurred after ablation for atypical flutter. One patient had undergone mitral valve replacement and tricuspid repair and presented with AF before surgery. Sinus rhythm was restored but later transitioned to right atrial incisional tachycardia. Another developed a prolonged tachycardia cycle with subsequent AF during ablation.

In the study group, a patient undergoing programmed ventricular stimulation with three extrastimuli developed ventricular fibrillation, which was successfully reverted to sinus rhythm with a single external defibrillation attempt. All complications during the early postoperative period are shown in Table 4.

In both groups, pulsating hematomas in the upper third of the right thigh were identified the day after RFA: one in the control group after AV node ab-

Table 2.

Types of Surgical Interventions in Patients with CIED

Type of surgical intervention	Study group	Control group
AV node ablation, n (%)	69 (51.5)	45 (71.4)
RFA of atrial fibrillation, n (%)	21 (15.7)	5 (7.9)
RFA of ventricular tachycardia, n (%)	5 (3.7)	2 (3.2)
RFA of RVOT tachycardia, n (%)	7 (5.2)	-
RFA of typical atrial flutter, n (%)	13 (9.7)	7 (11.1)
RFA of atypical atrial flutter, n (%)	7 (5.2)	1 (1.6)
RFA of ventricular ectopy, n (%)	6 (4.5)	2 (3.2)
RFA of ventricular fibrillation, n (%)	1 (0.7)	-
RFA of accessory pathways in WPW syndrome, n (%)	2 (1.5)	-
RFA of supraventricular ectopy, n (%)	2 (1.5)	-
RFA of inappropriate sinus tachycardia, n (%)	1 (0.7)	1 (1.6)
Catheters in a chamber with an implanted EL, n (%)	94 (70.1)	53 (84.1)
Total number, n	134	63

Note: Hereinafter, AV – Atrioventricular; RFA -Radiofrequency ablation; RVOT - Paroxysmal reciprocating AV nodal tachycardia; AP - Accessory pathways; EL - Endocardial lead.

Figure 1. Non-fluoroscopic catheter ablation of left ventricular tachycardia in a patient with an implanted cardioverter-defibrillator using transseptal access and a steerable introducer: a - Intracardiac ultrasound visualization; b - Surface ECG and endograms; c - Electroanatomical 3D map of the left ventricle.

lation and one in the study group after RFA for AF. Both cases were successfully treated conservatively with manual compression under ultrasound guidance within the first four hours of diagnosis.

A pericardial effusion (0.4 cm) was detected the day after AV node ablation in one study group patient and treated conservatively. Non-RFA-related complications included hematomas in the CIED pocket in three study group patients who underwent simultaneous pacemaker implantation and AV node ablation. All were on anticoagulant therapy and successfully managed conservatively. A left-sided pneumothorax was diagnosed in a study group patient who also underwent simultaneous pacemaker implantation and AV node ablation. The pneumothorax was resolved by draining the left pleural cavity.

DISCUSSION

Non-fluoroscopic RFA is the standard (routine) approach for interventional treatment of arrhythmias at the Federal Center of Cardiovascular Surgery in Krasnoyarsk. At the time of preparing this study, the center had performed over 5,000 non-fluoroscopic interventions. Considering the growing population of patients with CIED and the expanding indications for RFA, it was not surprising that patients with CIED requiring RFA began to emerge. Interventions for these patients were performed as experience in non-fluoroscopic procedures increased in the general population.

The main concerns were related to the risk of damage or dislodgement of ELs, especially in patients dependent on cardiac pacing. Cases of pacing disruption during RFA and external cardioversion have been described in the literature[12]. However, in all reported cases, the external defibrillator electrodes were placed over the CIED.

In our experience, no CIED malfunctions were identified in any of the 11 patients who underwent external cardioversion or the one patient who underwent defibrillation. In one case, ventricular lead dislodgement occurred six days after pacemaker implantation and eight hours after RFA of the AVN. After the RFA, the pacemaker was immediately reprogrammed to DDDR mode in the operating room, and no pacing dysfunction was detected. Pacing parameters remained unchanged after the RFA. Moreover, a mandatory examination one hour post-procedure (a standard practice in our center) also found no issues with pacemaker function, and the patient's heart rate at the time of examination was 65 bpm. Thus, the association between ventricular lead dislodgement and the performed RFA remains debatable.

When performing electroanatomical 3D reconstruction using navigation systems without intracardiac ultrasound visualization, it is not possible to precisely determine the position of ELs and their proximity to the ablation catheter. In this study, no difficulties were encountered with catheter manipulation within the heart chambers, entanglement with ELs, or fixation in subvalvular structures or trabeculae. This may be attributed to the algorithm developed and implemented at our center for performing RFA in patients with CIED.

Preoperative preparation for RFA in patients with CIED must include reviewing chest X-rays to identify the EL placement (a standard for patients scheduled for interventional electrophysiology procedures). It is advisable to separate the timing of CIED implantation and subsequent RFA by at least three months to reduce the risk of EL dislodgement during RFA or in the early postoperative period.

To enhance safety, the use of ablation catheters equipped with force-sensing technology to monitor tissue contact pressure is recommended. Such devices have recently become more commonly adopted in clinical practice. EL extraction or catheter withdrawal should always be performed in a straightened configuration to avoid accidental entanglement with the ELs, which could lead to dislodgement. During intracardiac manipulations, excessive rotational movements (over 1800° in one direction) should be avoided to prevent catheter entanglement with the ELs. A practical approach may involve removing the catheter and reinserting it in a neutral position.

In cases where catheter extraction from heart chambers proves difficult due to entanglement, ultrasound or fluoroscopic visualization is recommended. When planning RFA in heart chambers with implanted ELs near the implantation site, fluoroscopy (switching to a fluoroscopy-controlled procedure) may be necessary to assess the distance between the ablation catheter and the EL. This is particularly important for patients entirely dependent on cardiac pacing.

For recently implanted CIED requiring RFA with a high risk of ventricular EL dislodgement, it may be prudent to consider placing a "backup" diagnostic lead in the right ventricular cavity. Most patients in the study group underwent procedures without direct vi-

Table 3.

Duration of surgical interventions in patients with CIED

AV node ablation, min	Study group	Control group
RFA of atrial fibrillation, min	58,4±37,3	60,3±28,2
RFA of ventricular tachycardia, min	93,3±39,2	146±23,3
RFA of RVOT tachycardia, min	108±20,4	82,5±2,5
RFA of typical atrial flutter, min	98±29,9	-
RFA of atypical atrial flutter, min	84,8±28	115,7±34,6
RFA of ventricular ectopy, min	165±59,9	90
RFA of ventricular fibrillation, min	87,5±24,7	82,5±12,5
RFA of accessory pathways in WPW syndrome, min	230	-
RFA of supraventricular ectopy, min	80±20	-
RFA of unusual sinus tachycardia, min	150±30	-
RFA of atypical sinus tachycardia, min.	70	40

sualization of ELs, raising particular concerns for patients with cardiac resynchronization devices (CRTs), where the left ventricular lead is implanted in the coronary sinus system. No advantages of non-fluoroscopic RFA would outweigh the risk of left ventricular lead dislodgement, which would necessitate reimplantation and its associated risks. However, no issues with left ventricular leads were observed in either group.

Procedure duration was comparable between the groups for RFA of AF, typical AFL, and AVNA. In the study group, procedure times for AF and typical AFL were shorter than in the control group. This was primarily due to the use of a recently implemented high-power (50W), short-duration (9–14 seconds) RFA technique and ablation indices for linear lesions, which significantly reduced ablation times. These methods were applied to a larger proportion of patients in the study group compared to the control group. Other stages of RFA for AF and AFL were similar in duration between the groups.

In other cases, comparisons were not possible due to the small number of patients for each condition. Further prospective, randomized controlled studies are required to better understand the issue and establish unified guidelines for performing RFA in patients with CIED.

Table 4.

Complications in the early postoperative period after RFA of tachyarrhythmias in patients with CIED

Type of complication	Study group	Control group
Lead dislodgement		1
Pericardial effusion	1	
CIED pocket hematoma	3	
Pulsating thigh hematoma	1	1
Pneumothorax	1	

CONCLUSION

Non-fluoroscopic RFA of tachyarrhythmias in patients with CIED is both effective and safe. Special caution should be exercised when performing RFA in patients with implanted cardiac resynchronization devices, where the left ventricular lead is placed in the coronary sinus system, as well as in patients with CIED implanted less than six months prior. In such cases, the risk of lead dislodgement may outweigh the benefits of the non-fluoroscopic approach. Using intracardiac ultrasound visualization for the manipulation of ablation and diagnostic catheters in heart chambers with implanted ELs can significantly reduce the risk of adverse events. However, this requires additional venous access and increases the cost of the non-fluoroscopic RFA procedure. Prior to performing RFA for tachyarrhythmias, it is essential for the operator to have precise knowledge of the position of the endocardial leads and the patient's dependence on the pacemaker.

REFERENCES

1. Page RL, Joglar JA, Caldwell MA, et al. Guideline for the management of adult patients with supraventricular tachycardia: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2016;133: e471-505.

2. Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias-executive summary: a report of the American College of Cardiology/American HeartAssociation Task Force on Practice Guidelines and the European Society of CardiologyCommittee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation.* 2003;108: 1871-909.

3. Lundqvist CB, Potpara TS, Malmborg H. Supraventricular arrhythmias in patients with adult congenital heart disease. *Arrhythm Electrophysiol Rev.* 2017;6: 42-9.

4. Kovoor P, Ricciardello M, Collins L, et al. Radiation exposure to patient and operator during radiofrequency ablation for supraventricular tachycardia. *Aust N Z J Med.* 1995;25: 490-5.

5. Sarkozy A, De Potter T, Heidbuchel H, et al. ESC Scientific Document Group. Occupational radiation exposure in the electrophysiology laboratory with a focus on personnel with reproductive potential and during pregnancy: A European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS). *Europace.* 2017;19: 1909-22.

6. Buxton AE, Calkins H, Callans DJ, et al. American College of Cardiology; American Heart Association Task Force on Clinical Data Standards; (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). *J Am Coll Cardiol*. 2006;48: 2360-96.

7. Mah DY, Miyake CY, Sherwin ED, et al. The use of an integrated electroanatomic mapping system and intracardiac echocardiography to reduce radiation exposure in children and young adults undergoing ablation of supraventricular tachycardia. *Europace.* 2014;16: 277-83.

8. Casella M, Pelargonio G, Dello Russo A, et al. "Near-zero" fluoroscopic exposure in supraventricular arrhythmia ablation using the EnSite NavX™ mapping system: Personal experience and review of the literature. *J Interv Card Electrophysiol.* 2011;31: 109-18.

9. Giaccardi M, Del Rosso A, Guarnaccia V, et al. Near-zero x-ray in arrhythmia ablation using a 3-dimensional electroanatomic mapping system: A multicenter experience. *Heart Rhythm.* 2016;13: 150-6.

10. Stec S, Sledź J, Mazij M, et al. Feasibility of implementation of a "simplified, No-X-Ray, no-lead apron, two-catheter approach" for ablation of supraventricular arrhythmias in children and adults. *J Cardiovasc Electrophysiol* 2014;25: 866-74.

11. Yang L, Sun G, Chen X, et al. Meta-analysis of zero

or near-zero fluoroscopy use during ablation of cardiac arrhythmias. *Am J Cardiol.* 2016;118: 1511-8.
12. Kalbfeisch S, Daoud E, Humel J. Failure of Ventricular Capture from a Modern Generation CRT-ICD during Radiofrequency Ablation. *Pacing and Clinical Electrophysiology.* 2011; 36(6): 775-777.

https://doi.org/10.35336/VA-1305

FACTORS ASSOCIATED WITH DEATH IN PATIENTS WITH ATRIAL FIBRILLATION

S.P.Duvanova, L.V.Khoroshavtseva, E.V.Gorbunova, S.E.Mamchur, O.L.Barbarash
Research Institute of Complex Issues of Cardiovascular Diseases, Russia, Kemerovo, 6 Sosnovy blvd.

The aim of the study was to analyze the factors influencing the mortality prognosis for atrial fibrillation (AF) among the adult population of the Kuzbass region.

Methods. 576 patients with AF were included in the study. During a three-year follow-up death was recorded in 54 (9.4%) patients. An analysis of factor s associated with mortality was carried out. Multiple logistic regression, Quasi-Newton measurement method, ROC analysis were used, the critical significance level was 0.05.

Results. According to the conducted study data, a statistically significant increase in the chance of a fatal outcome was revealed in individuals with a history stroke (odds ratio (OR) 2.47 [1.06-5.75]), with a body mass index (BMI) equal to or higher than 32.4±6.8 kg/m^2 (OR 1.07 [1.01-1.14]), with an increase in the ventricular rate (VR) of AF equal to or higher than 84.2±15.4 beats per minute (OR 1.02 [1.00-1.04]) and the risk of thromboembolic complications according to the CHA_2DS_2VASc scale equal to or higher than 4.3±2.3 points (OR 1.12 [1.04-1.21]). A decrease in creatinine clearance (CC) according to Cockcroft-Gault was associated with a high risk of adverse outcome (OR 0.99 [0.98-1.00]). At the same time, the fact of irregular intake of anticoagulant therapy was associated with a high probability of death, but did not depend on which anticoagulant was prescribed.

Conclusions. According to the results of a complex analysis it was revealed that patients with AF who have a history of stroke, high values of BMI, ventricular rate AF, CHA_2DS_2VASc were more often having an unfavorable outcome.

Key words: predictors; fatal prognosis; atrial fibrillation; stroke; body mass index

Conflict of Interests: none.
Funding: none.
Received: 04.11.2023 **Revision Received:** 17.09.2024 **Accepted:** 08.10.2024
Corresponding author: Gorbunova Elena, E-mail: e.v.gorbunova@yandex.ru

S.P.Duvanova - ORCID ID 0000-0002-4348-3423, L.V.Khoroshavtseva - ORCID ID 0000-0001-7996-3501, E.V.Gorbunova - ORCID ID 0000-0002-2327-2637, S.E.Mamchur - ORCID ID 0000-0002-8277-5584, O.L.Barbarash - ORCID ID 0000-0002-4642-3610

For citation: Duvanova SP, Khoroshavtseva LV, Gorbunova EV, Mamchur SE, Barbarash OL. Factors associated with death in patients with atrial fibrillation. *Journal of Arrhythmology.* 2024;31(4): 24-28. https://doi.org/10.35336/VA-1305.

Atrial fibrillation (AF) is the most common arrhythmia, affecting 2.04% of the population in the European part of the Russian Federation**.** While AF is observed in only 0.1% of adults aged 20–29 years, its prevalence increases to 9.6% among individuals aged 80–89 years [1]. The medical literature does not provide a definitive consensus on whether the increased risk of mortality is associated with the severity of the tachyarrhythmia itself, the underlying and/or concomitant diseases, or irregular medication intake, which has been shown to increase the risk of adverse outcomes by 1.5–2 times [2, 3]. The causes of death in patients with AF include malignancies (23.1%), infectious complications (17.3%), congestive heart failure (14.5%), with stroke accounting for only 6.5% of cases [4]. Identifying predictors of mortality and developing strategies for its prevention are therefore of significant importance. This underscores the relevance of this study, which aimed to analyse the factors influencing fatal outcomes in patients with AF among the adult population of the Kuzbass region.

METHODS

A cohort of patients diagnosed with AF (n=576) was randomly selected for this study. These patients, all aged over 18 years, were managed on an outpatient basis at the polyclinic of the Research Institute of Complex Issues of Cardiovascular Diseases between 2019 and 2022. None of the patients met the criteria for interventional treatment of arrhythmias. During a three-year prospective follow-up period, mortality was documented in 54 patients (9.4%) based on statistical records from the ARENA Medical Information System. The recorded causes of death included myocardial infarction in 26 patients, acute cerebrovascular accident (stroke) in 16 patients, and acute heart failure in 12 patients. This study was conducted in compliance with the principles outlined in the Helsinki Declaration of the World Medical Association regarding “Ethical Principles for Medical Research Involving Human Subjects”.

Statistical Analysis

For the prospective analysis of quantitative indicators, the mean value (M) and standard deviation (σ) were calculated. Differences in quantitative indicators were assessed using the Mann-Whitney test for normally distributed variables, determined by the Kolmogorov-Smirnov test.

Multiple logistic regression and the Quasi-Newton estimation method were employed to analyse factors associated with mortality in patients with AF. If logistic regression

demonstrated significance, the baseline performance parameters (sensitivity and specificity, at a threshold value of 0.5), as well as the B coefficient, standard error, p-value, odds ratio (OR) with a 95% confidence interval (CI), and Wald chi-square were calculated separately for the constant and each predictor. A mathematical formula was derived using the B coefficients of predictors and the constant to determine the probability of an adverse outcome (death) for a patient.Statistical analysis was performed using R programming language (v.4.0.3), Python (v.3.8.3), and Statistica 6.0 software.

The quality of the resulting model (classifier) was evaluated using the following indicators: sensitivity (the number of deceased patients correctly classified divided by the total number of deceased patients), specificity (the number of surviving patients correctly classified divided by the total number of surviving patients), and AUC (Area Under the Curve). AUC served as an indicator of the model's effectiveness based on ROC analysis. For AUC values, the standard error and 95% CI boundaries were determined. The critical significance level was set at 0.05.

Table 1.

Characteristics of the studied patients with atrial fibrillation (n=576)

Indicators	Deceased (n=54)	Survivors (n=522)	P-level
Age, years	69.7±8.8	67.4±8.7	0.0652
Male, n (%)	29 (53.7%)	211 (40.4%)	0.0595
Female, n (%)	25 (46.3%)	311 (59.6%)	0.0595
Body Mass Index, kg/m^2	32.4±6.8	30.3±6.0	0.0160
Heart Rate during AF, bpm	84.2±15.4	79.2±15.7	0.0260
Systolic BP, mmHg	130±19.2	128±17.5	0.4286
Diastolic BP, mmHg	81±13.4	80±12.4	0.5758
Hospitalisations, n (%)	32 (59.3%)	265 (50.7%)	0.2345
Paroxysmal AF, n (%)	20 (37.0%)	259 (49.6%)	0.0783
Persistent AF, n (%)	21 (38.9%)	144 (27.6%)	0.0803
Permanent AF, n (%)	13 (24.1%)	119 (22.8%)	0.8317
CAD, n (%)	31 (57.4%)	235 (45.0%)	0.0822
Myocardial Infarction, n (%)	10 (18.5%)	52 (9.9%)	0.0534
ACVA, n (%)	10 (18.5%)	37 (7.1%)	0.0350
Hypertension, n (%)	50 (92.6%)	484 (92.7%)	0.9726
Morisky-Green Scale, points	2.6±1.7	2.5±1.4	0.6250
CC (Cockcroft-Gault), mL/min	77.0±25.6	83.4±28.2	0.1100
CHA_2DS_2VASc Score, points	4.3±2.3	3.5±1.9	0.0041
2MACE Score, points	2.1±1.2	1.8±1.1	0.0591
Warfarin, n (%)	21 (38.9%)	176 (33.7%)	0.5442
Rivaroxaban, n (%)	14 (25.9%)	153 (29.3%)	0.6018
Apixaban, n (%)	13 (24.1%)	120 (23.0%)	0.8570
Dabigatran, n (%)	6 (11.1%)	73 (14.0%)	0.5590

Note: Hereinafter, AF - Atrial fibrillation; BP - Blood pressure; CAD - Coronary artery disease; ACVA - Acute cerebrovascular accident (stroke); CC - Creatinine clearance.

RESULTS

A comparative analysis of gender and clinical-anamnestic data between deceased and surviving patients AF was conducted, as presented in Table 1. It was found that patients with fatal outcomes were characterised by statistically significantly higher values of body mass index (BMI), ventricular rate (VR) during AF, more frequent occurrences of acute cerebrovascular accidents (stroke), and higher CHA_2DS_2VASc scores.

Clinical-anamnestic data were evaluated at the inclusion stage of the study to identify factors associated with mortality in patients with AF (Table 2). These factors included: gender, age (years), BMI (kg/m^2), VR (beats per minute), systolic and diastolic blood pressure (mmHg), history of hospitalisation, type of AF (paroxysmal, per-

Table 2.

Predictors of fatal outcomes in patients with atrial fibrillation

Indicator	Coefficient B	SE	p-level	OR	CI-	CI+	Wald Chi-Square
Gender	0.67	0.36	0.059	1.96	0.97	3.95	3.58
ACVA	0.90	0.43	0.035	2.47	1.06	5.75	4.44
CAD (MI)	0.72	0.42	0.08	2.05	0.91	4.65	2.98
Body Mass Index	0.07	0.03	0.016	1.07	1.01	1.14	5.86
Ventricular Rate	0.02	0.009	0.026	1.02	1.00	1.04	4.97
Creatinine Cleara	-0.01	0.007	0.11	0.99	0.98	1.00	2.52
CHA_2DS_2VASc Score	0.11	0.04	0.004	1.12	1.04	1.21	8.22
2MACE Score	0.22	0.12	0.059	1.24	0.99	1.56	3.59
Constant	-6.76	1.24	<0.0001	0.001	0.0001	0.013	29.62

Note: Hereinafter, B coefficient - Regression coefficient; SE - Standard error; OR - Odds ratio; CI- and CI+ - Lower and upper bounds of the 95% confidence interval for the odds ratio; MI - Acute Myocardial Infarction.

sistent, permanent), presence of coronary artery disease (CAD), cerebrovascular accident (stroke), hypertension (HTN), adherence to treatment assessed by the Morisky-Green questionnaire (points), creatinine clearance (CC) based on the Cockcroft-Gault formula (mL/min), CHA_2DS_2VASc score (points), and 2MACE score (points). Additionally, the impact of anticoagulant use on the prognosis of AF progression was also assessed.

The overall characteristics of the constructed model demonstrated its effectiveness. Pearson's Chi-Square value was 42.1, with a p-value of 0.0001, indicating statistical significance. Regression coefficients were utilised to develop a classification model for predicting patient outcomes based on the following formula:

$$Y1 = EXP(Z1) / (1 + EXP(Z1)) \quad (1)$$

$$Z1 = -6{,}76 + (X1 \times 0{,}67) + (X2 \times 0{,}90) + (X3 \times 0{,}72) + (X4 \times 0{,}07) + (X5 \times 0{,}02) + (X6 \times -0{,}01) + (X7 \times 0{,}11) + (X8 \times 0{,}22),$$

where: Y_1: The probability of a fatal outcome for a patient, ranging from 0 to 1. If the calculated value is less than 0.5, the model predicts patient survival; if the value is 0.5 or higher, the model predicts a fatal outcome; X_1: Gender (0 = female, 1 = male); X_2: History of cerebrovascular accident (stroke) (0 = no, 1 = yes); X_3: Presence of coronary artery disease (0 = no, 1 = yes); X_4: Body mass index (BMI, kg/m²); X_5: Ventricular rate (VR, beats per minute); X_6: Creatinine clearance (CC, mL/min) calculated by the Cockcroft-Gault formula; X_7: CHA2DS2VASc score (points); X_8: 2MACE score (points).

According to the analysis, patients with AF who had a history of cerebrovascular accidents (strokes), a BMI of ≥32.4±6.8 kg/m², a ventricular rate of ≥84.2±15.4 bpm during AF, or a CHA_2DS_2VASc score of ≥4.3±2.3 points were statistically significantly more likely to experience mortality (Fig. 1 and 2).

The area under the ROC curve AUC was 0.76 [0.70–0.82], indicating a good-quality classifier. Through the ROC analysis, an optimal cut-off threshold for the model was determined, with balanced levels of specificity (0.71) and sensitivity (0.70), reflecting good classification capability for predicting patient outcomes.

The study identified a statistically significant increase in the likelihood of adverse outcomes in individuals with a history of stroke (OR 2.47 [1.06-5.75]). As BMI (OR 1.07 [1.01-1.14]), ventricular rate during AF (OR 1.02 [1.00-1.04]), and CHA_2DS_2VASc score (OR 1.12 [1.04-1.21]) increased, the probability of a fatal outcome also rose.

Additionally, a non-significant direct association was observed between the dependent variable and the presence of coronary artery disease (OR 2.05 [0.91-4.65], p = 0.08), as well as the 2MACE score (OR 1.24 [0.99-1.56], p = 0.059). There was also a tendency towards increased mortality risk in male patients (OR 1.96 [0.97-3.95], p = 0.059).

Furthermore, the Creatinine Clearance by Cockcroft-Gault variable showed a negative association with adverse AF outcomes (OR 0.99 [0.98-1.00]). However, no statistically significant relationship was found between the type of prescribed oral anticoagulant and mortality.

DISCUSSION

Thus, in patients with AF and a history of cerebrovascular accidents (strokes), higher BMI values, increased ventricular rate (VR) during AF, and elevated CHA_2DS_2VASc scores were associated with higher mortality rates. Conversely, the presence of CAD and male gender were associated with a lower likelihood of adverse outcomes in patients with AF.

Numerous international and Russian studies have examined risk factors related to the likelihood of developing ischaemic stroke and other thromboembolic complications [5]. However, only a limited number of studies have focused on predictors of mortality. An analysis of the REK-VASA-AF registry (Kursk) identified factors associated with adverse outcomes through multivariate analysis, such as age, VR of 90 bpm or more, and a history of myocardial infarction (MI) [6].

In the AMADEUS study, absolute rates of stroke, systemic embolism, cardiovascular mortality, or any clin-

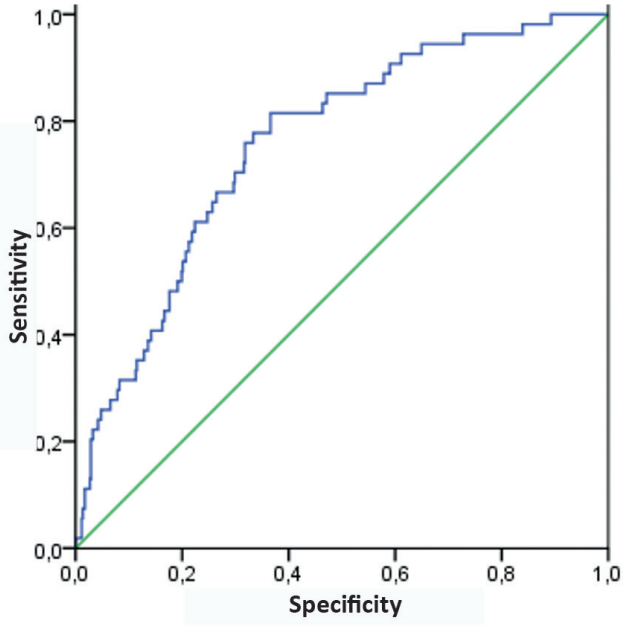

Figure 1. ROC Curve for Predicting Outcomes in Patients with Atrial Fibrillation.

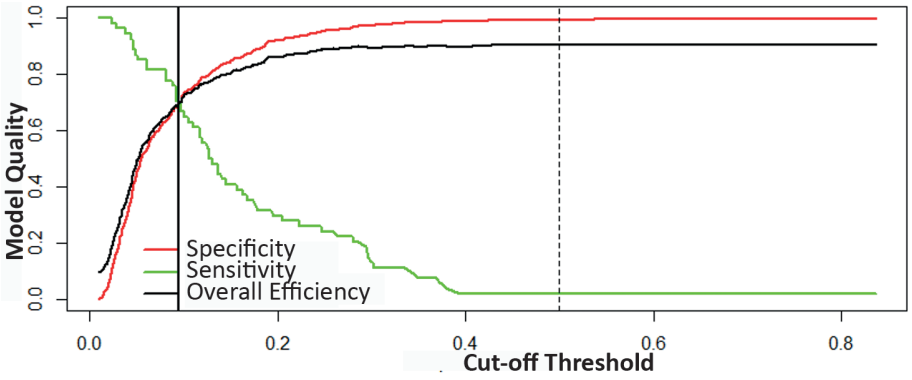

Figure 2. Dependence of the Model's Key Characteristics on the Cut-off Threshold Value.

ically significant bleeding were higher in patients aged over 75 years [7]. According to M.V.Solovieva's research [8], no specific oral anticoagulant significantly influenced mortality outcomes; however, disruptions in anticoagulant therapy regimens or discontinuation of medication were significantly associated with worse long-term outcomes, increasing the risks of composite endpoints (recurrent MI + stroke + cardiovascular mortality).

The Italian MATISS project found that VR was an independent predictor of cardiovascular and overall mortality [9]. In contrast, N.G.Vinogradova's study [10] on mortality predictors in patients with AF combined with chronic heart failure (CHF) demonstrated that tachycardia was not an independent predictor of death; instead, a higher functional class of CHF increased the mortality risk.

According to S.Wu et al. [11], in patients with AF aged 65–75 years and older, the risk of death was significantly lower in those with overweight or obesity compared to patients younger than 65 years, in whom increasing BMI was associated with higher mortality risk.

In O.P.Mamaeva's study [12], risk factors for cardiovascular mortality were evaluated in patients with persistent AF who were not on anticoagulants. Irregular anticoagulant use and failure to achieve the target INR range were associated with a high risk of thrombotic and haemorrhagic complications. The primary risk factors for mortality were tachycardia and a history of stroke, which aligns with the findings of our study.

CONCLUSION

It was found that in patients with AF, mortality occurred more frequently in those with a history of stroke, BMI of 32.4±6.8 kg/m², VR during AF of 84.2±15.4 bpm, and CHA_2DS_2VASc scores ≥4.3±2.3. It can be assumed that knowledge of these identified predictors of mortality will facilitate the development of a comprehensive set of measures aimed at preventing adverse outcomes. The correction of modifiable risk factors and adherence to prescribed therapy could help prevent severe cardiovascular complications, improve quality of life, preserve work capacity, and enhance longevity in patients with AF.

REFERENCES

1. Mareev YuV, Polyakov DS, Vinogradova NG, et al. Epidemiology of atrial fibrillation in a representative sample of the European part of the Russian Federation. Analysis of EPOCH-CHF study. *Kardiologiia.* 2022;62(4): 12-19. (In Russ.). https://doi.org/10.18087/cardio.2022.4.n1997.

2. Ardashev AV, Belenkov YuN, Matsiukevich MC, et al. Atrial Fibrillation and Mortality: Prognostic Factors and Direction of Prevention. *Kardiologiia*. 2021;61(2): 91-98. (In Russ.). https://doi.org/10.18087/cardio.2021.2.n1348.

3. Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, et al. European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *J Arrhythm*. 2020;36(4): 553-607. https://doi.org/10.1002/joa3.12338.

4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal* 2020;00:1-125. https://doi.org/10.1093/eurheartj/ehaa612.

5. Kadikov AS, Shahparonova NV. Modern prevention of primary and recurrent ischemic strokes. The role of antiplatelet therapy. *RMM.* 2013; 30: 1603. (In Russ.).

6. Mikhin VP, Maslennikova YuV, Lukyanov MM, et al. Structure of mortality and evaluation of death risk in patients with combination of atrial fibrillation and coronary heart disease (RECVASA AF-KURSK registry data). *Man and his health.* 2017;(4): 35-41. (In Russ.). https://doi.org/10.21626/vestnik/2017-4/07.

7. Senoo K, Lip GY. Relationship of Age with Stroke and Death in Anticoagulated Patients With Nonvalvular Atrial Fibrillation: AMADEUS Trial. *Stroke*. 2015; 46(11): 3202-3207. https://doi.org/10.1161/STROKEAHA.115.010614

8. [Soloveva MV, Boldueva SA. Antithrombotic therapy and its impact on prognosis in patients with atrial fibrillation and myocardial infarction. Long-term observation results. *Cardiosomatics*. 2021;12 (3): 158-165. (In Russ.). https://doi.org/10.26442/22217185.2021.3.201044.

9. Seccareccia F, Pannozzo F, et al. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health*. 2001; 91(8): 1258-1263. https://doi.org/10.2105/ajph.91.8.1258.

10. Vinogradova NG, Polyakov DS, Fomin IV, et al. Prognosis of the life of patients with chronic heart failure and atrial fibrillation, depending on the control of hemodynamic parameters and tolerance to physical exertion in the background of basic therapy. *Kardiologiia*. 2019; 59(4S): 51-58. (In Russ.). https://doi.org/10.18087/cardio.2622.

11. Wu S, Yang YM, Zhu J, et al. Impact of age on the association between body mass index and all-cause mortality in patients with atrial fibrillation. *J Nutr Health Aging.* 2017; 21(10): 1125-1132. https://doi. org/10.1007/s12603-016-0863-2.

12. Mamaeva OP, Egorov DF, Podlesov AM, et al. Risk factors of cardiovascular death in patients with permanent atrial fibrillation. *Journal of Arrhythmology*. 2008; 52(52): 45-49. (In Russ.).

https://doi.org/10.35336/VA-1398

ENDOCARDIAL LEAD IMPLANTATION IN PATIENTS WITH VEIN ACCESS OBSTRUCTION

S.A.Aivazian[1], I.N.Sorokin[1], A.A.Palagina[1], A.A.Seregin[1], A.N.Shamatolskiy[2]

[1]Volga regional medical center FMBA, Russia, Nizhny Novgorod, 2 Nizhnevolzhskaya emb.;

[2]SBHI of the Nizhny Novgorod Region «Research Institute - Specialized Cardiac Surgery Clinical Hospital named after acad. B.A.Korolev», Russia, Nizhny Novgorod, 209 Vaneeva str.

Aim. To present the experience of lead implantation in patients with cardiac implantable electronic devices (CIED) and access veins stenoses/occlusions, evaluate the effectiveness and safety of different methods and propose a decision-making algorithm for the method of new lead implantation in such patients.

Methods. The study includes 31 patients with CIED and access veins obstruction, which required implantation of new leads. Leads were implanted after recanalization of the veins with hydrophilic wires through long introducers, or after transvenous lead extraction (TLE) using TightRail sheath.

Results. Recanalization of veins using guidewires followed by lead implantation through a long introducer was performed in 24 patients, in 9 of them, after recanalization as the second step during the same procedure, TLE was performed. TLE without preliminary recanalization with guidewire was performed in 5 patients. In two patients, leads were implanted after vein puncture medial to the occlusion. Successful new leads implantation was performed in all patients. Decision making algorithm for the method of leads implantation through obstruction veins in various clinical situations is proposed.

Conclusions. Recanalization of occluded veins with guidewire and TLE in patients with CIED are effective methods for providing ipsilateral access for lead implantation through obstructed veins. The safety of TLE in patients with access vein obstruction requires further study.

Key words: venoplasty; implantable cardiac electronic devices; venous obstruction; venous recanalization; transvenous lead extraction

Conflict of Interest: none.
Funding: none.
Received: 20.08.2024 **Revision received:** 04.11.2024 **Accepted:** 21.11.2024
Corresponding author: Aivazian Sergey, E-mail: sergei_aivazyan@mail.ru

S.A.Aivazian - ORCID ID 0000-0002-9642-9754, I.N.Sorokin - ORCID ID 0000-0002-7350-8353, A.A.Palagina - ORCID ID 0000-0001-8233-6664, A.A.Seregin - ORCID ID, A.N.Shamatolskiy - ORCID ID 0000-0003-2453-9257

For citation: Aivazian SA, Sorokin IN, Palagina AA, Seregin AA, Shamatolskiy AN. Endocardial lead implantation in patients with vein access obstruction. *Journal of Arrhythmology.* 2024;31(4): 29-37. https://doi.org/10.35336/VA-1398.

Obstruction of access veins through which leads are implanted is one of the most common complications in patients with cardiac implantable electronic devices (CIEDs). This issue becomes particularly acute for patients requiring lead replacement due to dysfunction or the addition of new leads for more complex device implantation. In the largest study to date, Czajkowski M. et al. retrospectively analyzed 3,002 venographies in patients who subsequently underwent transvenous lead extraction (TLE). The study found moderate vein stenosis (50–80%) in 20.7% of patients, significant stenosis (>80%) in 19.9%, and complete vein occlusion in 22.5%. Thus, venous access difficulties may occur in 60% of patients requiring lead replacement or the addition of new leads [1].

In most cases, obstruction of veins within the superior vena cava (SVC) is asymptomatic due to the formation of an extensive collateral network that provides satisfactory blood drainage from the upper extremities. Vein occlusion is generally detected intraoperatively when lead replacement or addition is required. Antegrade venography via the cubital, subclavian, or axillary veins is useful for determining the location and extent of occlusion or stenosis [2].

For addressing vein obstruction, several techniques are available. Implantation of the entire system on the contralateral side is a straightforward approach; however, it necessitates the placement of additional leads, which can lead to contralateral vein occlusion and superior vena cava syndrome over time [3, 4]. Another approach is implanting leads on the contralateral side and connecting them to the device in the original pocket, tunneling the lead subcutaneously. This method carries similar drawbacks to the first technique [5].

Vein puncture medial to the occlusion or stenosis is another option, although it presents an elevated risk of pneumothorax. Over time, this approach may result in lead fractures caused by damage between the clavicle and the first rib [6]. Antegrade vein recanalization using a guidewire is also employed, and some authors recommend supplementing it with balloon angioplasty to ensure proper venous outflow from the extremity [7, 8]. The “inside-out” technique involves retrograde vein recanalization with the externalization of a guidewire at the site of occlusion [9].

Device implantation via femoral or iliac vein access is an alternative when lead placement through SVC basin veins is not feasible. However, this method carries a higher risk of infection at the CIED pocket site and thrombotic complications in the inferior vena cava (IVC) basin. Moreover, it requires longer-than-standard leads [10]. Epicardial lead implantation is another method, though its main drawback is its invasiveness [11]. The use of leadless pacemakers, which are not yet registered in the Russian Federation, represents another potential solution [12].

A significant limitation of these approaches is the presence of residual non-functional leads, which may lead to severe complications over time [13, 14]. TLE offers the advantage of simultaneously removing non-functional leads and performing vein recanalization for the implantation of new leads [15–17]. However, TLE carries a considerable risk of serious complications, including myocardial and major vein injury [18, 19]. Currently, there is no standardized approach for managing patients with access vein occlusions requiring pacing and/or defibrillation due to lead dysfunction or the need for a more complex device.

The aim of this study is to present our experience with lead implantation in patients with obstructed access veins, evaluate the effectiveness and safety of various techniques, and propose a decision-making algorithm for selecting the appropriate method for new lead implantation.

METHODS

This retrospective study included 31 patients with previously implanted CIEDs who, between January 2017 and December 2023, required the implantation of new leads due to the obstruction of veins through which the leads were originally implanted. For these patients, standard lead implantation was not feasible.

Standard lead implantation was defined as puncture of the axillary vein with an 18G needle, insertion of a 0.035” metal guidewire, placement of a peel-away introducer (7–9 Fr, 12 cm in length) over the guidewire, and implantation of the lead through the introducer, or implantation through the cephalic vein. For all patients with CIEDs requiring new lead implantation, venography was performed via a peripheral vein.

Computed tomography (CT) of the chest with contrast enhancement was performed in five patients to clarify the anatomical features of occlusive and stenotic lesions of the subclavian, brachiocephalic veins, and SVC, as well as to determine the position of leads within these veins (Fig. 1a).

Compromised leads were defined as those connected to the CIED at the time of surgery but rendered non-functional or prone to complications for various reasons: fractured leads; leads with high stimulation and/or defibrillation thresholds; leads with impaired sensitivity; leads causing ulceration at the pocket site due to looping; leads implanted during childhood positioned in the right ventricle as loops and inducing ventricular arrhythmias.

Abandoned leads were defined as implanted leads disconnected from the CIED: previously disabled, severed, or capped.

Vein recanalization with a guidewire

After venography via the cubital vein, puncture of the axillary vein was performed using an 18G needle. A 0.035” metal guidewire was advanced to the site of occlusion/stenosis. A dilator from a 5 Fr introducer or a 5 Fr introducer (12 cm in length) was advanced over the guidewire into the vein. Venography was repeated through the dilator or introducer. The metal guidewire was replaced with a hydrophilic guidewire. Preferred guidewires included the Roadrunner 0.035” (140 mm, COOK, USA), Hi-Torque Command 0.014” (Abbot, USA), or V-18 (Boston Scientific, USA). For complex cases, Corsair microcatheters (ASAHI, Japan) were used. After traversing the stenosis/occlusion, the guidewire was advanced into the right atrium, and a 23 cm-long introducer was positioned across the stenosis/occlusion. Contrast was injected through the introducer to confirm its tip placement within the vein or right atrium beyond the occlusion. A new lead was then implanted through the introducer.

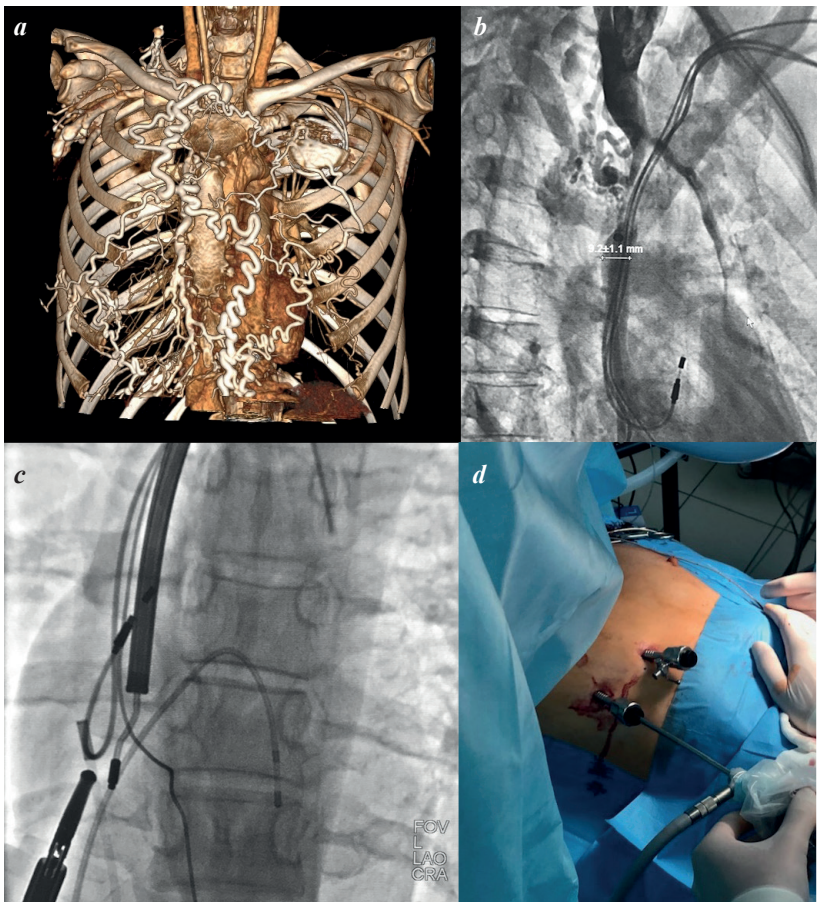

Figure 1. Video-assisted transvenous lead extraction (TLE) for a patient with superior vena cava (SVC) occlusion: a - computer tomography scan of the chest, developed collaterals visualisation; b - venography; c - TLE and recanalization SVC; d - ports for video thoracoscopy.

For patients requiring angioplasty, an 8×40 mm or 8×60 mm balloon catheter (Sterling, Boston Scientific, USA) was advanced over the guidewire post-recanalization. The balloon was inflated at the stenosis site to 8–12 atm. Balloon venoplasty was performed in cases of difficult lead manipulation or delivery device navigation across extensive occlusions.

For patients with SVC occlusion, venography was performed with simultaneous antegrade and retrograde contrast injection. Catheters were positioned in the right internal jugular vein and the proximal SVC via femoral access. Additional venography through the left axillary vein was performed as needed. This technique allowed detailed visualization of the extent and configuration of SVC occlusion and helped determine the optimal trajectory for guidewire advancement (Fig. 1b).

For patients with low risk of lead extraction, successful guidewire recanalization was followed by TLE using locking stylets, rotational dilators, and transfemoral lead extraction. TLE risks were assessed using the RISE protocol, Kancharla K. et al., and EROS scales [20–22].

Transvenous Lead Extraction Method

TLE was performed under total intravenous anesthesia with mechanical ventilation. All procedures were conducted by a cardiovascular surgeon prepared for immediate conversion to open surgery. Invasive arterial pressure monitoring was maintained via radial or femoral artery access. The target lead was dissected from scar tissue up to its entry into the subclavian/axillary vein. The connector portion was severed, leaving a 7–8 cm segment of the lead body. A locking stylet (LLD EZ or LLD 2, Spectranetics, USA) was advanced into the lead lumen. Rotational dilators (TightRail 11–13 Fr, Spectranetics, USA) were used to free the lead from fibrous encapsulation, simultaneously recanalizing the vein.

If the lead dislodged from the heart chamber during extraction before the vein occlusion was traversed, a triple-loop snare (EnSnare, Merit, USA) was introduced via femoral access to capture the lead tip and hold it in the right atrium. Recanalization was then completed with TightRail, followed by lead implantation (Fig. 2). Lead fragments resulting from TLE were removed with a triple-loop snare or a two-loop snare (Needle's Eye Snare, COOK Medical, USA) via femoral access.

For patients with SVC occlusion, hybrid video-assisted transvenous lead extraction was performed to minimize the risk of fatal complications associated with SVC injury [23] (Fig. 1). Following TLE, leads were implanted via the axillary vein to prevent future lead fractures, using standard access techniques [24]. Guidewires advanced through the rotational dilator lumen served as a safety backup.

Statistical Analysis

All data were recorded in Excel tables (Microsoft, 2021). Categorical variables were presented as absolute values and percentages. Continuous variables were assessed for normality and presented as medians with interquartile ranges, expressed as Me [Q1; Q3], as all continuous variables were found to deviate from normal distribution.

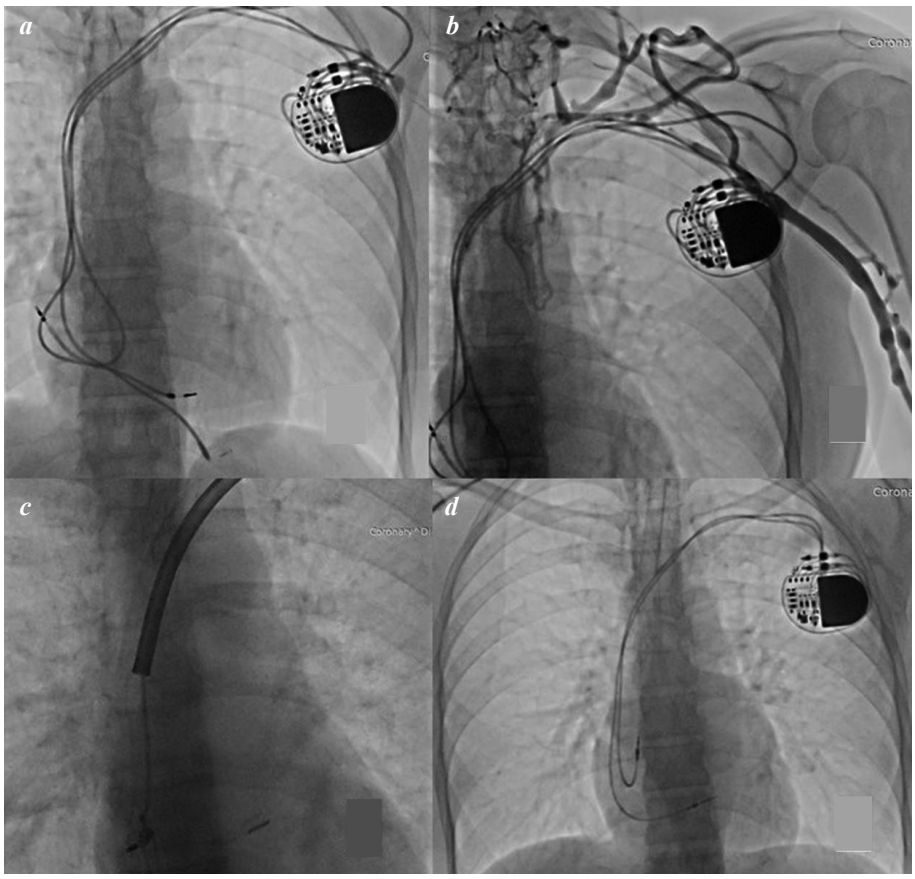

Figure 2. Extraction of broken lead with recanalization of occluded vein and new lead implantation. a - initial chest X-ray; b - venography, revealed occlusion of subclavian and innominate veins; c - fixation of the lead with endovascular snare system, femoral access for recanalization of the vein with a rotary dilator, d - chest X-ray after procedure, implanted new leads.

RESULTS

New lead implantation was performed in 149 patients with previously implanted CIEDs. Among them, 122 patients had compromised leads, and 27 required new leads for the implantation of a more advanced device. In 31 patients (21.5%), venous access obstruction or significant stenosis was identified. Cases involving reimplantation of devices after removal due to infection were excluded from the study.

The clinical characteristics of the patients included in the study are presented in Table 1. The median age of the patients was 65.5 [56.3; 72.0] years (range: 11 to 83 years). There were 18 female patients (56.3%). The median body mass index (BMI) was 26.6 [23.8; 29.7] kg/m². Three patients (9.7%) had previously undergone open-heart surgery (two coronary artery bypass grafting [CABG]

and one combined CABG and aortic valve replacement). The median left ventricular ejection fraction (LVEF) was 54.0 [48.3; 61.2]%.

The majority of patients had previously been implanted with dual-chamber pacemakers (64.5%). A small number of cases involved patients with implanted biventricular pacemakers or cardioverter defibrillators (Table 2). One patient had an implanted cardiac contractility modulator. The primary indication for surgery was lead dysfunction (high pacing thresholds or lead fracture) in 87% of cases. In two patients, new leads were implanted to upgrade the system to a dual-chamber device. The indication for surgery in the patient with a cardiac contractility modulator was impaired sensing of the left septal lead. It is noteworthy that seven patients had previously undergone three or more device-related surgeries. In three patients, the device had already been implanted on the contralateral side due to venous occlusion.

The median age of previously implanted leads was six [3; 9] years, ranging from one to 21 years. A high risk of TLE was identified in 16 (51.6%) patients with compromised leads based on the RISE scale, in eight (25.8%) patients based on the Kancharla scale, and in four (12.9%) patients based on the EROS scale (Tables 1, 2). These scales typically account for lead age, patient comorbidities, and the age at initial device implantation.

Venography revealed left subclavian vein obstruction in most cases (18 patients, 58%). Isolated severe stenosis/occlusion of the brachiocephalic vein was observed in eight (25.8%) patients. Isolated SVC occlusion was found in one (3.2%) patient. Extensive occlusions involving the subclavian, brachiocephalic veins, and SVC were identified in four (12.9%) cases.

Guidewire recanalization was performed in 24 (77.4%) patients. Long introducers were used for lead implantation in all cases. Balloon venoplasty was performed in only four (12.9%) cases. In 15 (48.4%) patients, lead extraction was not attempted due to the extremely high risk of TLE, attributed to lead age, comorbidities, or limited TLE experience at the time of intervention.

In nine (29%) patients, step-by-step TLE was performed as a second stage. All extracted leads were pacing leads. In four (12.9%) cases, leads were removed using traction with a locking stylet, in five (16.1%) cases using a rotational dilator, and in one (3.2%) case using a snare via femoral access. A total of 11 leads were extracted from this group of nine patients.

In five (16.1%) patients with venous occlusion, TLE was performed without prior guidewire recanalization. Rotational dilators were used for TLE in all these cases (Table 3). A total of 10 pacing leads were extracted in this group.

In one patient with SVC occlusion and a BMI of 18 kg/m², TLE was performed under thoracoscopic guidance. In two cases, femoral access was additionally utilized. In three cases, TLE was performed after failed guidewire recanalization, including one pediatric patient aged 11 years. In all these cases, new lead implantation was successfully performed via the axillary vein. Hydrophilic guidewires were advanced without technical difficulties through the

Table 1.

Clinical characteristics of patients with venous stenosis/occlusion

Total patients, n (%)	31 (100)
Age, years	60 [60; 75]
Age at initial implantation, years	59 [47; 69]
Female sex, n (%)	17 (54,8)
Body Mass Index, kg/m^2	26,6 [23,8; 29,7]
Heart failure (NYHA III-IV), n (%)	5 (16,1%)
Left ventricular ejection fraction, %	54,0 [48,3; 61,2]
History of open-heart surgery, n (%)	4 (12,9)
Atrial fibrillation, n (%)	8 (25,8)
Arterial hypertension, n (%)	15 (48,3)
Diabetes, n (%)	4 (12,9)
Chronic kidney disease (stage 3-4), n (%)	1 (3,2)
History of malignancy, n (%)	1 (3,2)
Number of procedures related to CIED, n (%)	2 [1; 3]
According to the RISE scale, n (%)	
According to the Kancharla K. et al. scale, n (%)	16 (51,6)
According to the EROS scale, n (%)	8 (25,8)
Total patients, n (%)	4 (12,9)

Note: CIED - cardiac implanted electronic device

Table 2.

Device characteristics and indications for surgery

Total devices, n (%)	31 (100)
AAIR P, n (%)	2 (6.5)
VVIR P, n (%)	6 (19.4)
DDDR P, n (%)	20 (64.5)
CRT-P, n (%)	1 (3.2)
ICD DR, n (%)	1 (3.2)
CRT-D, n (%)	0 (0)
CCM, n (%)	1 (3.2)
Number of compromised leads, n	41
Age of compromised leads, years	7 [4-12]
Indications for implantation of a new lead	
Mode switch from AAIR to DDDR, n (%)	2 (6.5)
Severe pain syndrome, n (%)	1 (3.2)
Lead loop in the RVOT, n (%)	1(3.2)
Lead dysfunction, n (%)	27(87.1)

Note: Hereinafter, P - Pacemaker; CRT-P - Biventricular pacemaker; ICD - Implantable cardioverter-defibrillator; CRT-D - Biventricular ICD; CCM - Cardiac contractility modulator; RVOT - Right ventricular outflow tract.

channel created by the rotational dilator into the right heart chambers. Subsequently, the safety guidewires inserted through the rotational dilator channel were removed.

Vein puncture medial to the subclavian vein occlusion was used for new lead implantation in two cases: once after unsuccessful guidewire recanalization and once without attempting recanalization. This method was used as an exception due to the high long-term risk of lead fracture associated with implantation from this access point.

In total, unnecessary leads were removed in 14 (48.2%) patients with compromised leads. New lead implantation via the axillary vein was performed in 29 (93.5%) patients. Successful new lead implantation through occluded/stenotic veins was achieved in all patients. None required lead implantation through contralateral veins or alternative methods.

Minor complications occurred in five (16.1%) cases (Table 4). During TLE, non-target functioning leads were damaged and/or dislodged in four patients, necessitating their removal and new lead implantation. In one case, the postoperative period was complicated by a hematoma at the CIED pocket site following lead removal with a rotational dilator, requiring pocket revision. No major complications or fatalities occurred in this patient cohort following TLE.

This experience allowed us to develop and propose a decision-making algorithm for patients with CIEDs and venous access obstruction requiring new lead implantation (Fig. 3).

Table 3.

Types of procedures in patients

Medial puncture of SV, n (%)	2 (6.5)
RG, n (%)	15 (48.3)
RG + balloon angioplasty, n (%)	4 (12.9)
RG and TLE (step-by-step), n (%)	9 (29.0)
- Traction with LS, n (%)	4 (12.9)
- RD, n (%)	5 (16.1)
- RD + FA, n (%)	1 (3.2)
TLE only, n (%)	5 (16.1)
- RD, n (%)	4 (12.9)
- RD + thoracoscopy, n (%)	1 (3.2)
- RD + FA, n (%)	3 (9.7)
Total procedures, n (%)	31(100)
RD in all cases, n (%)	10 (32.3)
FA in all cases, n (%)	4 (12.9)

Note: Hereinafter, SV - Subclavian vein; RG - Recanalization with a guidewire; TLE - Transvenous lead extraction; LS - Locking stylet; RD - Rotational dilator; FA - Femoral access.

Table 4.

Procedure results

Number of patients who underwent lead implantation, n (%)	31 (100)
Number of patients who underwent TLE, n (%)	14 (45.2)
Number of patients without retained leads, n (%)	14 (45.2)
Number of patients with retained leads, n (%)	17 (54.8)
Number of implanted leads, n	40
Number of removed leads, n	21
Number of retained non-functional leads, n	20
Complications	
Dislocation/damage to non-target lead, n (%)	4 (12.9)
Hematoma at the pocket site requiring reoperation, n (%)	1 (3.2)
Operative mortality, n (%)	0 (0)

DISCUSSION

A search of the MEDLINE/PubMed database identified over 10 different approaches for addressing venous stenosis/occlusion in patients with CIEDs [5-12]. This diversity highlights the lack of a universal solution for these patients. In routine clinical practice, the most commonly used method involves implanting new leads and devices on the contralateral side without removing compromised leads.

Contralateral lead implantation can eventually result in bilateral venous obstruction within the SVC or SVC syndrome [3, 4]. In cases of SVC occlusion, epicardial lead implantation is a more invasive method with a shorter lifespan for epicardial leads compared to endocardial leads [25]. Implanting leads via femoral/iliac veins is associated with a higher risk of infectious complications.

Based on our experience, guidewire recanalization is an effective and safe technique. Successful advancement of a hydrophilic guidewire through the stenosis/occlusion was achieved in 77.4% of cases. In facilities lacking expertise in TLE, guidewire recanalization followed by lead implantation using a long introducer may be a preferred approach. This technique can be further complemented by balloon venoplasty.

Lead implantation through occluded veins following TLE has been recognized in several studies as an effective and safe method, with the added advantage of removing compromised leads. However, most specialists approach TLE cautiously, given its association with serious complications and mortality [13, 14, 18, 19]. Nevertheless, in high-volume centers performing over 30 TLEs annually, the rates of major complications and mortality are minimal [26]. Based on our experience of over 200 TLEs, we consider leads older than 10 years as high risk, consistent with the Kancharla scale [21]. For patients with SVC-related occlusion/stenosis caused by leads, TLE is the method of choice for providing access for new lead implantation [27].

Our experience with guidewire recanalization and TLE suggests that combining these techniques is optimal and both should be available in a clinic's repertoire. We were highly cautious in using TLE without prior guidewire recanalization, employing this approach in only two cases.

The first case involved a 35-year-old female patient with a BMI of 18 kg/m², third-de-

gree atrioventricular block, SVC occlusion, and a fractured ventricular lead. The patient had three leads in the heart chambers. Hybrid thoracoscopically-assisted TLE was performed, removing the atrial and ventricular leads implanted five years ago while leaving and sealing a lead implanted 12 years ago.

The second case involved a 74-year-old male patient with bilateral subclavian and brachiocephalic vein occlusion, SVC occlusion, and a fractured ventricular lead implanted five years ago. The lead was removed with transfemoral assistance, and a new lead was implanted.

In our clinical practice, TLE decisions are carefully balanced between risk and benefit, guided by TLE risk scales. Even with this measured approach, we performed TLE in 14 patients with venous occlusions, including nine patients who underwent successful guidewire recanalization as a first step.

Why aim to perform TLE in as many patients as possible? This stems from a desire to minimize the number of non-functional leads and from the expertise accumulated in our clinic, which helps reduce complication risks.

Our primary goal was to implant new leads. Once venous access for lead implantation was secured, we proceeded with TLE, prepared to stop at any point and leave the lead if necessary. Expanding TLE experience and using risk scales in our clinic have allowed us to broaden TLE indications for patients with venous occlusions. In high-risk cases, guidewire recanalization is recommended; for low and intermediate risks, TLE can be performed.

The proposed algorithm attempts to systematize methods for lead implantation in patients with venous access obstruction. However, numerous other factors must be considered, including lead model, availability of a complete TLE toolkit, anesthetic protocol nuances, the ability for immediate conversion to open surgery, and the patient's life expectancy.

TLE risk is challenging to determine in some cases. Risk assessment scales, such as the RISE protocol or MB score, where leads younger than five years indicate low TLE risk, can help reduce the number of abandoned leads [28].

A drawback of removing compromised leads is the risk of damaging or dislodging functional leads. This risk must also be considered when planning TLE, and the necessary leads and consumables should be readily available, particularly for patients with biventricular devices.

A limitation of implanting new leads through guidewires advanced via rotational dilator channels is the repeated use of the subclavian vein, as most extracted leads were implanted via this access. This approach increases the risk of lead fractures, especially when the reason for re-operation is an existing lead fracture. For this reason, all new leads were implanted via the axillary vein. After TLE, hydrophilic guidewires were advanced without technical difficulties through channels formed by rotational dilators into the right heart chambers, serving as a safety backup.

For short subclavian vein occlusions, vein puncture medial to the occlusion is a possible venous access option. We employed this technique in two cases but subsequently abandoned it due to the high risk of pneumothorax and long-term lead fracture.

Study Limitations

A significant limitation of our study is the small number of patients with biventricular devices and cardioverter-defibrillators. This reflects the low number of such patients under observation in our clinic. According to the literature, patients with multi-lead systems are most frequently affected by venous access obstruction.

CONLUSION

Guidewire recanalization of occluded veins and transvenous lead extraction in patients with cardiac implantable electronic devices are effective and safe methods for providing ipsilateral access for lead implantation in cases of lead dysfunction or when a change in pacing mode is required. These techniques help avoid device implantation on the contralateral side. We believe it is essential for specialists performing device implantations to master vein recanalization methods and for operating rooms to be equipped with the necessary tools.

TLE reduces the number of abandoned leads. The choice of method depends on the level of TLE expertise in each clinic. TLE risk assessment scales can assist in decision-making, and the algorithm we propose may prove useful in daily practice.

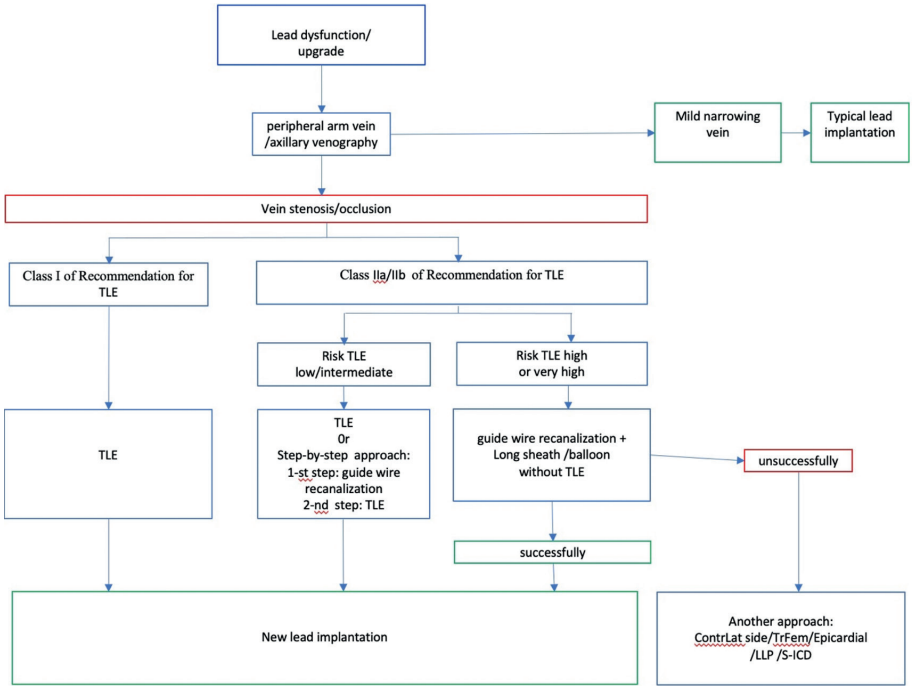

Figure 3. Deciding algorithm on the method of lead implantation in non-infection patients with vein obstruction. TLE - transvenous lead extraction; ContrLat - contralateral; TrFem - transfemoral; LLP - leadless pacemaker; S-ICD - subcutaneus implantable cardioverter-defibrillator.

In cases where vein recanalization is unsuccessful and TLE is not feasible, one of the following approaches should be considered, taking into account the clinic's capabilities and the patient's comorbidities: epicardial lead implantation, implantation via femoral/iliac veins, leadless pacemaker implantation, or subcutaneous cardioverter-defibrillator implantation. In our study, the use of these methods was successfully avoided.

REFERENCES

1. Czajkowski M, Jacheć W, Polewczyk A, et al. Severity and Extent of Lead-Related Venous Obstruction in More Than 3000 Patients Undergoing Transvenous Lead Extraction. *Vasc Health Risk Manag.* 2022;18: 629-642. https://doi.org/10.2147/VHRM.S369342.
2. Albertini CMM, Silva KRD, Filho L, et al. Usefulness of preoperative venography in patients with cardiac implantable electronic devices submitted to lead replacement or device upgrade procedures. *Arq Bras Cardiol*. 2018;111(5): 686-696. https://doi.org/10.5935/abc.20180164.
3. Gabriels J, Chang D, Maytin M, et al. Percutaneous management of superior vena cava syndrome in patients with cardiovascular implantable electronic devices. *Heart Rhythm.* 2021 Mar;18(3):392-398. https://doi.org/10.1016/j.hrthm.2020.11.012.
4. Arora Y, Carrillo RG. Lead-related superior vena cava syndrome: Management and outcomes. *Heart Rhythm.* 2021;18(2): 207-214. https://doi.org/10.1016/j.hrthm.2020.09.006
5. Lüthje L, Zabel M, Seegers J, et al. Acute and long-term feasibility of contralateral transvenous lead placement with subcutaneous, pre-sternal tunnelling in patients with chronically implanted rhythm devices. *Europace*. 2011;13: 1004-1008. https://doi.org/10.1093/europace/eur072.
6. Antonelli D., Freeddberg N., Turgeman Y. Supraclavicular vein approach to overcoming ipsilateral chronic subclavian vein obstruction during pacemaker-ICD lead revision or upgrading. *Europace.* 2010;12: 1596-1599. https://doi.org/10.1093/europace/euq314.
7. Marcial JM, Worley SJ. Venous System Interventions for Device Implantation. *Card Electrophysiol Clin.* 2018 Mar;10(1):163-177. https://doi.org/10.1016/j.ccep.2017.11.017.
8. Worley SJ, Gohn DC, Pulliam RW, et al. Subclavian venoplasty by the implanting physicians in 373 patients over 11 years. *Heart Rhythm.* 2011;8(4): 526-533. https://doi.org/10.1016/j.hrthm.2010.12.014.
9. Elayi CS, Allen CL, Leung S, et al. Inside-out access: a new method of lead placement for patients with central venous occlusions. *Heart Rhythm.* 2011;8: 851-857. https://doi.org/10.1016/j.hrthm.2011.01.024.
10. Griffiths S, Behar JM, Kramer DB, et al. The long-term outcomes of cardiac implantable electronic devices implanted via the femoral route. *Pacing Clin Electrophysiol.* 2022;45(4): 481-490. https://doi.org/10.1111/pace.14449.
11. Kar AK, Ghosh S, Majumdar A, et al. Venous obstruction after permanent pacing. Indian Heart J. 2000;52(4): 431-3.
12. Ekizler FA, Ozeke O, Okten RS, et al. Change from Cardioinhibitory Syncope to Iatrogenic Positional Syncope: Superior Vena Cava Syndrome Treated by Superior Vena Cava Stenting and Leadless Pacemaker Implantation. *J Innov Card Rhythm Manag.* 2018;9(9): 3312-3314. https://doi.org/10.19102/icrm.2018.090902.
13. Segreti L, Rinaldi CA, Claridge S, et al. Procedural outcomes associated with transvenous lead extraction in patients with abandoned leads: an ESC-EHRA ELECTRa (European Lead Extraction ConTRolled) Registry Sub-Analysis. *Europace*. 2019;21(4): 645-654. https://doi.org/10.1093/europace/euy307.
14. Elgaard AF, Johansen JB, Nielsen JC, et al. Long-term follow-up of abandoned transvenous defibrillator leads: a nationwide cohort study. *Europace*. 2020;22(7): 1097-1102. https://doi.org/10.1093/europace/euaa086.
15. Witte OA, Adiyaman A, van Bemmel MW, et al. Mechanical power sheath mediated recanalization and lead implantation in patients with venous occlusion: Technique and results. *J Cardiovasc Electrophysiol*. 2018;29(2): 316-321. https://doi.org/10.1111/jce.13389.
16. Al-Maisary S, Romano G, Karck M, et al. The use of laser lead extraction sheath in the presence of supra-cardiac occlusion of the central veins for cardiac implantable electronic device lead upgrade or revision. *PLoS One.* 2021;16(5): e0251829. https://doi.org/10.1371/journal.pone.0251829.
17. Brar V, Worley SJ, Eldadah Z, et al. "Retained wire femoral lead removal and fibroplasty" for obtaining venous access in patients with refractory venous obstruction. *J Cardiovasc Electrophysiol.* 2021;32(10): 2729-2736. https://doi.org/10.1111/jce.15197.
18. Lee JZ, Ling J, Diehl NN, et al. Mortality and Cerebrovascular Events After Heart Rhythm Disorder Management Procedures. *Circulation*. 2018 ;137(1):24-33. https://doi.org/10.1161/CIRCULATIONAHA.117.030523.
19. Bongiorni MG, Kennergren C, Butter C, et al. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) Registry of Transvenous Lead Extraction Outcomes. *Eur Heart J.* 2017;38(40): 2995-3005. https://doi.org/10.1093/eurheartj/ehx080.
20. Afzal MR, Daoud EG, Matre N et al. Risk Stratification prior to lead Extraction and impact on major intraprocedural complications (RISE protocol). *J Cardiovasc Electrophysiol.* 2019;30(11): 2453-2459. http://https://doi.org/10.1111/jce.14151.
21. Kancharla K, Acker NG, Li Z, et al. Efficacy and safety of transvenous lead extraction in the device laboratory and operating room guided by a novel risk stratification scheme. *JACC Clin Electrophysiol*. 2019;5: 174-82. http://https://doi.org/10.1016/j.jacep.2019.01.001.
22. Sidhu BS, Ayis S, Gould J, et al. Risk stratification of patients undergoing transvenous lead extraction with the ELECTRa Registry Outcome Score (EROS): An ESC EHRA EORP European lead extraction ConTRolled ELECTRa registry analysis. *EP Eur.* 2021;23: 1462-1471. http://https://doi.org/10.1093/europace/euab037.
23. Ajvazyan SA, Grishin IR, Emelyanov AV, et al. Method for removing endocardial electrodes under the videothoracoscopy control in patients with high risk of damage to the superior vena cava system. Abstract of invention RU

2743616 C1, 20.02.2021. Application № 2020118670 от 28.05.2020 (In Russ.).
24. Burri H, Starck C, Auricchio A, et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). *Europace*. 2021;23(7): 983-1008. https://doi.org/10.1093/europace/euaa367.
25. Medtronic CRM Product Perfomance Report. 2023. 1st Edition. Issue 88 Available from https://wwwp.medtronic.com/productperformance/model/4968-capsure-epi.html
26. Issa ZF. Transvenous lead extraction in 1000 patients guided by intraprocedural risk stratification without surgical backup. *Heart Rhythm.* 2021;18(8): 1272-1278. https://doi.org/10.1016/j.hrthm.2021.03.031.
27. Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm.* 2017; 14(12):e503-51. http://https://doi.org/10.1016/j.hrthm.2017.09.001
28. Bontempi L, Curnis A, Della Bella P, et al. The MB score: a new risk stratification index to predict the need for advanced tools in lead extraction procedures. *Europace*. 2020;22: 613-621 http://doi:10.1093/europace/euaa027.

https://doi.org/10.35336/VA-1392

PREDICTORS OF EARLY ARRHYTHMIA RECURRENCE AFTER ATRIAL FIBRILLATION CATHETER ABLATION

T.V.Moskovskih, A.V.Smorgon, S.Yu.Usenkov, E.A.Archakov, E.S.Sitkova, R.E.Batalov, S.I.Sazonova
Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Russia, Tomsk, 111a Kievskaya str.

Aim. Search for predictors of early recurrence of atrial tachyarrhythmias after radiofrequency ablation (RFA) of atrial fibrillation (AF).

Methods. The study included 57 subjects with persistent (n = 17; 30%) and paroxysmal (n = 40; 70%) forms of AF, admitted for the RFA. All patients underwent transthoracic echocardiography, assessment of deformation of both atria using 2D Strain, computed tomography (CT) with 3D reconstruction of the left atrium (LA). Intraoperatively, high-density voltage mapping of LA was performed before RF pulmonary vein isolation. All patients underwent follow-up after 3 months.

Results. Recurrence of atrial tachyarrhythmia after 3 months was recorded in 17.5% of patients. High prevalence of low-amplitude activity zones in the LA and persistent AF were the strongest predictors. The LA reservoir function below 21.7%, the conduction function below 15.7%, the LA stiffness index above 0.314 relative units, the LA volume with the appendage above 121.7 ml, and the LA vertical size according to CT data above 65.5 mm statistically significantly predicted early recurrences of atrial tachyarrhythmias with high sensitivity and specificity.

Conclusion. The decreased LA deformation in the reservoir and conductor phase, increased LA stiffness index, the prevalence of low-amplitude activity zones, vertical size and volume of the LA with an auricle according to CT data and persistent AF are significant predictors of early relapses after interventional treatment of AF.

Key words: atrial fibrillation; catheter ablation; left atrium; right atrium; atrial fibrosis; atrial deformation; high density mapping.

Conflict of Interest: none.
Funding: none.
Received: 11.08.2024 **Revision received:** 13.11.2024 **Accepted:** 28.11.2024
Corresponding author: Moskovskih Tatiana, E-mail: moskovskih_tanya@mail.ru

T.V.Moskovskih - ORCID ID 0000-0002-8689-8493, A.V.Smorgon - ORCID ID 0000-0002-6531-7223, S.Yu.Usenkov - ORCID ID 0000-0001-9553-9647, E.A.Archakov - ORCID ID 0000-0002-2530-361X, E.S.Sitkova - ORCID ID 0000-0002-0988-3642, R.E.Batalov - ORCID ID 0000-0003-1415-3932, S.I.Sazonova - ORCID ID 0000-0003-2799-3260

For citation: Moskovskih TV, Smorgon AV, Usenkov SYu, Archakov EA, Sitkova ES, Batalov RE, Sazonova SI. Predictors of early arrhythmia recurrence after atrial fibrillation catheter ablation. *Journal of Arrhythmology.* 2024;31(4): 38-46. https://doi.org/10.35336/VA-1392.

Atrial fibrillation (AF) is a widespread cardiac pathology, and its incidence is predicted to increase in the coming decades. This rise is expected to contribute to higher rates of disability and cardiovascular mortality among the adult working population [1]. The cardiology community is focused on identifying medical and surgical treatment methods that can reduce the progression of AF and eliminate this type of arrhythmia in patients [2]. In many arrhythmology centres, catheter ablation (CA) is the primary treatment method for AF, including as a first-line therapy. However, despite advancements in interventional techniques, the recurrence rate of arrhythmias, particularly early recurrences, remains significant [3].

When determining the treatment strategy for an AF patient, clinicians evaluate factors such as left ventricular (LV) systolic function, the presence of valvular pathology, atrial size, volume, and volume index, among others. Yet, even in the absence of significant structural heart changes, early recurrences of atrial tachyarrhythmias frequently occur during the three-month "blanking" period following CA or immediately after its completion, often persisting during subsequent follow-up [4, 5].

Atrial remodelling during AF is characterized by altered contractility and elasticity of myocardial fibres, which may precede structural changes detectable through imaging modalities like echocardiography (Echo) or computed tomography (CT) [6]. The Speckle Tracking Imaging (STE) 2D Strain ultrasound technology enables the assessment of myocardial mechanical function. Numerous studies have demonstrated the predictive value of left atrial (LA) deformation during the reservoir phase in forecasting CA outcomes [7].

In recent years, high-density electrophysiological voltage mapping, an intraoperative method for indirectly assessing myocardial fibrosis, has been increasingly adopted in clinical practice. This technique analyses the amplitude of bipolar signals from atrial tissue. International studies have shown that this technology can predict CA

outcomes [8] and provide a personalized approach to arrhythmia substrate modification [9]. Thus, the search for more sensitive predictors of early post-CA recurrences, which would allow for an individualized approach to catheter-based and pharmacological treatment in different patient categories, remains a pressing issue in the scientific cardiology community.

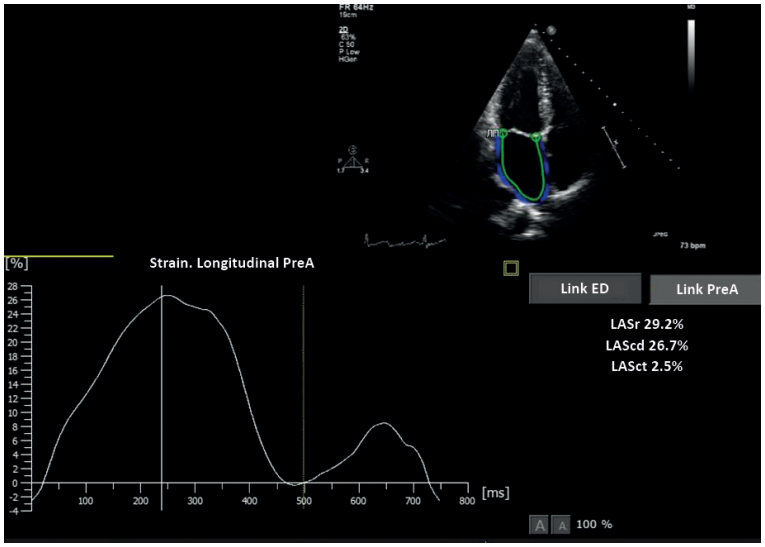

Figure 1. Longitudinal deformation of the left atrium. Note: LAScd - conductor function; LASct – contractile function; LASr – reservoir function;

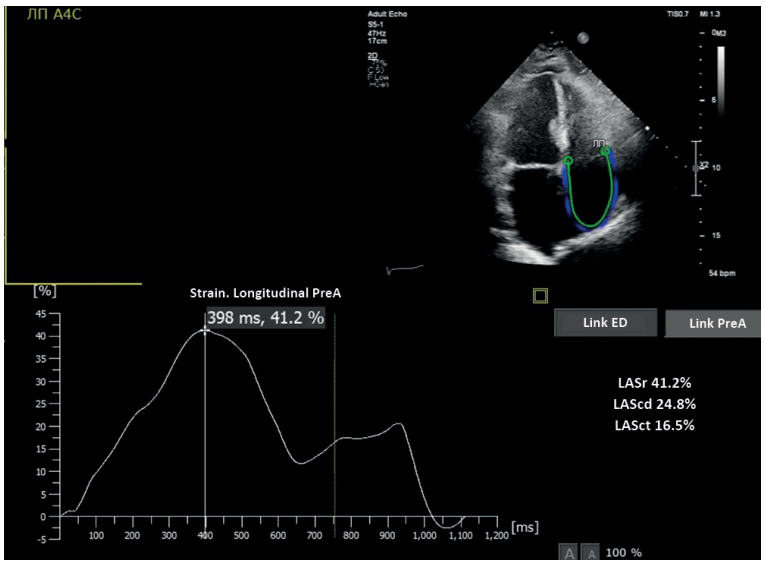

Figure 2. Longitudinal deformation of the right atrium.

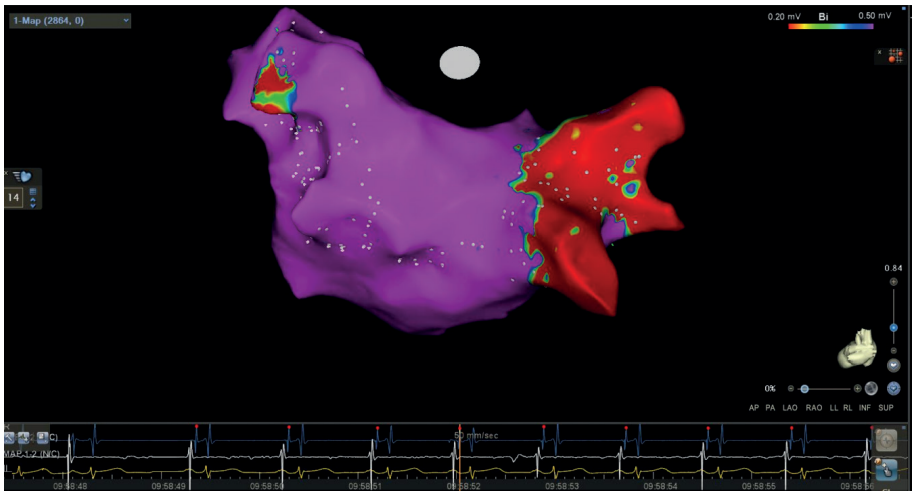

Figure 3. Electroanatomic voltage map of the left atrium, where the low-amplitude zone (less than 0.2 mV) is marked in red (area between the right pulmonary veins).

Aim. To identify predictors of early recurrences of atrial tachyarrhythmias after radiofrequency ablation (RFA) of atrial fibrillation.

METHODS

A single-centre, prospective, observational, non-randomized study was conducted. The study considered patients admitted to the Department of Surgical Treatment for Complex Cardiac Rhythm Disorders and Electrostimulation at the Cardiology Research Institute, Tomsk, for RFA of AF. Patients with prior RFA for any arrhythmia, valvular, coronary, or congenital heart pathologies, implanted devices, LV contractility impairment (ejection fraction [EF] below 50%, hypo- or akinesia), pulmonary arterial hypertension, or contraindications for RFA were excluded. Ultimately, 57 patients with paroxysmal (n=40; 70%) and persistent (n=17; 30%) forms of AF were included in the study, with a mean age of 55.4±9.8 years.

The study was conducted in accordance with clinical guidelines and the principles of the Declaration of Helsinki. Study protocol No. 205 was approved by the Biomedical Ethics Committee of the Cardiology Research Institute on December 8, 2020. All participants provided informed consent.

During hospitalization, in addition to standard clinical and instrumental examinations, CT with three-dimensional reconstruction of the LA was performed using a 64-detector CT scanner (GE Discovery NM/CT 570c, GE Healthcare, Milwaukee, WI, USA).

The deformation of both atria was assessed in all patients using transthoracic 2D Strain Echo from a four-chamber view on sinus rhythm with a Philips Affinity ultrasound scanner (USA). The P wave was used as the zero value. Image analysis was conducted offline with the Philips QLAB 15 software (USA). Endocardial and epicardial boundaries were manually marked at the end-systole of the LV and right ventricle, determined by the program. After confirmation, a longitudinal strain curve was constructed, including the peak longitudinal positive strain of the right atrium (Fig. 1) and the reservoir phase (positive strain at the end of LV systole), conductor phase (early diastole after mitral valve opening), and

contractile phase (negative strain during LV end-diastole) of LA strain (Fig. 2). The mean value across all segments was used as the final value [10]. Additionally, the left atrial stiffness index (LASI)—the ratio of E/E′ to global peak LA strain was calculated, reflecting increased filling pressures in the left heart chambers and indirectly indicating LA rigidity and fibrosis [11].

In the X-ray operating room, under intravenous sedation, high-density intracardiac voltage mapping of the LA was performed for all patients using a 20-pole PentaRay catheter (Biosense Webster Inc.) in sinus rhythm. Bipolar voltage maps were recorded and filtered at a frequency of 30-300 Hz, containing at least 3,000 points. Low-voltage zones were defined as areas with three or more points with a bipolar signal amplitude of less than 0.2 mV (Fig. 3). The CARTO 3 non-fluoroscopic system (Biosense Webster, USA) was used for the electroanatomical reconstruction of the LA [12].

Next, RFA with pulmonary vein (PV) isolation was performed using a NaviStar CoolFlow or SmartTouch ThermoCool ablation catheter (Biosense Webster, USA). The criterion for electrical isolation of the PVs was the disappearance of potentials on the circular Lasso electrode (Biosense Webster, USA) and confirmation of bidirectional conduction block during control pacing [13].

Following RFA, all patients received antiarrhythmic, anticoagulant, and therapy for underlying pathologies per clinical guidelines [1]. Follow-up was conducted three months after the RFA during a "blanking" period, during which patients' clinical conditions were assessed. Recurrence was defined as atrial tachyarrhythmias documented on an electrocardiogram (ECG) or 24-hour Holter ECG monitoring lasting more than 30 seconds and occurring during the three-month blanking period or persisting beyond its end. Based on the data analysis, patients were divided into two groups according to the presence of atrial tachyarrhythmia recurrence: Group 1 - without recurrence, and Group 2 - with recurrence within three months after RFA.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 26 (IBM Corporation, USA). The normality of distribution was checked using the Shapiro-Wilk test. Data were described as means with standard deviations (M±SD), medians with interquartile ranges (Me [Q25; Q75]), or absolute values with their percentages. Differences between independent samples were assessed using the Student's t-test or nonparametric Mann-Whitney U test. For paired samples, the paired Student's t-test was used, and for nominal indicators, the Pearson χ^2 test was applied. Logistic regression analysis was used to evaluate the prognostic significance of the methods. To compare the diagnostic efficacy of the methods studied in the work, Receiver Operating Characteristic (ROC) analysis was conducted. The informativeness of the diagnostic test was determined by calculating the area under the ROC curve (AUC) and finding the optimal cut-off value. Changes were considered statistically significant at a significance level of $p<0.05$.

RESULTS

During the 3-month follow-up period after RFA, atrial tachyarrhythmia recurrence was recorded in 10 patients, classified into the second observation group. Among these cases, ECG findings identified AF in seven patients, atrial tachycardia in two, and atrial flutter in one. The groups were comparable regarding sex, age, BMI, cardiovascular pathology, and arrhythmia duration, but patients with recurrence more often exhibited persistent AF (p=0.002). First-class antiarrhythmic drugs (propafenone, etacizine, or lappaconitine hydrobromide) were more frequently used in Group 1, whereas Group 2 predominantly received amiodarone (p=0.008). The clinical characteristics are presented in Table 1.

Table 1.

Clinical characteristics of patients, M±SD or Me [Q25;Q75]

Indicator	Group 1 (n=47)	Group 2 (n=10)	P
Men, n (%)	25 (53)	6 (60)	0.695
Age, years	54.9±10.2	58.1±6.92	0.344
BMI, kg/m²	29.8±5.33	30.3±6.36	0.801
Hypertension, n (%)	42 (89)	9 (90)	0.952
Coronary Artery Diseases, n (%)	14 (29.8)	4 (40)	0.528
Myocarditis, n (%)	2 (4.3)	1 (10)	0.460
Idiopathic AF, n (%)	4 (8.5)	0 (0)	0.339
Paroxysmal AF, n (%)	37 (79)	3 (30)	0.002
Persistent AF, n (%)	10 (21)	7 (70)	
AF Duration, months	12 [7.5; 48]	36 [14; 84]	0.269
CHF I FC, n (%)	7 (14.9)	1 (10)	0.686
CHF II FC, n (%)	5 (10.6)	2 (20)	0.413
EHRA, points	2 [2;2]	2 [1;2]	0.051
CHA_2DS_2-VASc, points	2 [1; 2]	3 [1; 4]	0.244
HAS-BLED, points	0 [0;0]	1 [0;1]	0.250
Antiarrhythmic Therapy*			
Amiodarone, n (%)	9 (19.1)	6 (60)	0.008
Sotalol, n (%)	15 (31.9)	2 (20)	0.455
Class 1C drugs, n (%)	23 (48.9)	2 (20)	0.094
β-blockers, n (%)	1 (2.1)	0 (0)	0.642
Anticoagulant Therapy			
Rivaroxaban, n (%)	18 (38.3)	2 (20)	0.271
Dabigatran, n (%)	8 (14)	4 (40)	0.106
Apixaban, n (%)	21 (44.5)	4 (40)	0.786

Note: hereinafter, BMI - Body Mass Index; AF - Atrial Fibrillation; CHF - Chronic Heart Failure; FC - Functional Class; CHA_2DS_2-VASc - Stroke Risk Score for Patients with AF; EHRA - European Heart Rhythm Association Score for Symptoms Associated with AF; HAS-BLED - Bleeding Risk Score for Patients with AF.

Echo comparisons revealed statistically significant differences: patients with recurrence showed larger vertical dimensions of both atria and higher LA volumes compared to those without recurrence. There were no significant intergroup differences in diastolic or systolic functions or LV size parameters. 2D Strain data indicated that LA deformation in the reservoir and conduction phases was higher in patients maintaining sinus rhythm, while the LA stiffness index was lower compared to Group 2. Right atrial (RA) deformation did not differ significantly between groups (Table 2).

CT findings showed that patients with atrial tachyarrhythmia recurrence had significantly larger LA volumes with appendage (137.2±21.2 ml vs. 109.1±22.8 ml, p=0.001), without appendage (119.5±21.2 ml vs. 100.0±20.7 ml, p=0.010), and vertical size (71.0 [65; 75.4] mm vs. 48.7 [41.0; 66.0] mm, p=0.023).

High-density voltage mapping identified low-amplitude activity zones in 19 patients. These were categorized into four subgroups: 1 (n=38) without low-amplitude zones in the LA, 2 (n=9) with zones covering <20% of LA area, 3 (n=5) with zones covering 20-30%, and 4 (n=5) with zones covering >30% of LA area. Persistent sinus rhythm was less frequently associated with low-amplitude activity zones (75% vs. 30%, p=0.007), and when present, the zones tended to be smaller. Most patients with atrial tachyarrhythmia recurrences belonged to subgroups with more extensive LA involvement.

Univariate and multivariate logistic regression analyses were conducted to assess predictors of early recurrences of atrial tachyarrhythmias after CA, focusing on parameters that showed statistically significant differences between groups (Table 3). Multivariate analysis highlighted persistent AF, the extent of low-amplitude activity zones, reservoir function, LA vertical size, and LA volume with appendage as the strongest predictors. Each predictor's significance was further evaluated using ROC analysis.

LA deformation during the reservoir phase demonstrated a significant inverse association with early recurrences (p=0.002), with an AUC of 0.807±0.091 (95% CI: 0.630-0.985). Patients with deformation <21.7% exhibited a high risk of recurrence, with 80% sensitivity and 91.5% specificity (Fig. 4).

LA volume with appendage showed a direct significant association (p=0.003), with a cut-off value of 121.8 ml (70% sensitivity and 71.4% specificity), characterized by an AUC of 0.806±0.074 (95% CI: 0.661-0.951) (Fig. 5).

CT-based LA vertical size was directly associated with recurrence risk (p=0.023), with a cut-off of 65.5 mm (71% sensitivity and 73% specificity), characterized by an AUC of 0.783±0.127 (95% CI: 0.661-0.951) (Fig. 5).

Although the LASI was not included in multivariate analysis, ROC analysis showed a direct association with early recurrences (p=0.003). The ROC curve demonstrated an AUC of 0.774±0.093 (95% CI: 0.592-0.957) (Fig. 5). LASI >0.314 relative units predicted recurrence risk with 70% sensitivity and 83% specificity.

Table 2.

Echocardiographic characteristics of patients, M±SD or Me [Q25;Q75]

Indicator	Group 1 (n=47)	Group 2 (n=10)	P
LV EF, %	67.0 [64.0; 69.0]	67.0 [64.0; 72.0]	0.636
LV EDV, ml	98.3±18.1	99.0±18.1	0.916
LV ESV, ml	33.0 [27.0; 37.0]	32.0 [24.0; 40.0]	0.898
LV EDI, ml/m^2	50.5±5.97	47.8±6.30	0.201
LV ESI, ml/m^2	16.7 ±3.16	15.6 ±3.55	0.321
LA APD, mm	39.5±3.50	41.1±4.36	0.199
LA Transverse Dimension, mm	43.0 [41.0; 44.0]	44.5 [41.0; 49.0]	0.163
LA Vertical Dimension, mm	53.4±4.09	57.0±4.47	0.016
LAV, ml	67.1 ±15.9	80.1±21.9	0.034
LAVI, ml/m^2	34.9±6.12	38.5±9.00	0.133
RA Transverse Dimension, mm	42.0 [40.0; 44.0]	43.0 [41.0; 47.0]	0.161
RA Vertical Dimension, mm	50.8±3.79	53.5±3.98	0.045
RAV, ml	68.3 [53.0; 74.2]	68.9 [66.0; 90.7]	0.157
RAVI, ml/m^2	32.5±5.45	35.6±6.70	0.121
RVSP, mmHg	27.0 [25.5; 29.0]	27.0 [25.0; 30.0]	0.831
LV MMI, g/m^2	81.0 [75.0; 85.0]	82.5 [75.0; 91.0]	0.443
E, cm/s	67.0 [60.5; 79.5]	69.5 [58.0; 80.0]	0.975
A, cm/s	70.5±14.7	71.4±5.41	0.840
E/A	0.87 [0.80; 1.25]	0.93 [0.83; 1.08]	0.925
e', cm/s	11.0 [9.00; 12.6]	10.0 [8.90; 11.5]	0.474
E/e'	6.52±1.38	7.08 ± 1.71	0.267
LA Reservoir Function, %	27.5 [24.8;30.0]	19.9 [18.3; 21.1]	0.002
LA Conduction Function, %	17.1 [14.0;20.3]	12.9 [10.4; 15.7]	0.033
LA Contractile Function, %	9.51±3.89	7.97±3.45	0.255
RA Longitudinal Strain, %	28.2±5.81	26.1±6.71	0.306
LA Stiffness Index, rel.u	0.235 [0.198; 0.289]	0.355 [0.266; 0.434]	0.007

Note: hereinafter, EDV - End-Diastolic Volume; ESV - End-Systolic Volume; LV - Left Ventricle; LA - Left Atrium; LAVI - Left Atrial Volume Index; LAV - Left Atrial Volume ; APD - Anterior-Posterior Dimension; RA - Right Atrium; RAVI - Right Atrial Volume Index; RAV - Right Atrial Volume; RVSP - Right Ventricular Systolic Pressure ; EF - Ejection Fraction; E peak - Early Diastolic Filling (Passive Filling Phase); A peak - Late Diastolic Filling (Active Filling Phase); E/A - Ratio of Passive to Active Filling Phases; e' - Velocity of Lateral Mitral Annular Motion (Tissue Doppler); E/e' - Ratio of Passive Filling Phase to Lateral Mitral Annular Velocity.

Similarly, conduction-phase LA deformation exhibited a significant inverse association with recurrences (p=0.033), characterized by an AUC of 0.716±0.096 (95% CI: 0.527-0.904) (Fig. 4). A deformation level <15.8% predicted high recurrence risk with 80% sensitivity and 63.8% specificity.

Three months post-CA, patients with early atrial tachyarrhythmia recurrences exhibited lower LA reservoir function (22.3% vs. 26.6%, p=0.004) and reduced RA longitudinal positive deformation (26.8% vs. 31.4%, p=0.036). These findings reflect ongoing atrial remodeling despite CA and may predict the persistence of arrhythmias beyond the blanking period, potentially necessitating repeat interventions.

DISCUSSION

In clinical practice, the development of atrial tachyarrhythmia paroxysms within the first three months after catheter treatment, the so-called "blanking period," is not considered indicative of an ineffective ablation. This can be attributed to inflammation, alterations in the autonomic nervous system functioning, and/or immaturity of the postoperative scar [3]. However, studies in the global literature have demonstrated the high prognostic value of early atrial arrhythmia recurrences, particularly during the third month after RFA, in predicting long-term CA outcomes [4, 5]. This evidence suggests the need to reconsider the timeframe for evaluating the expected effects of interventional AF treatment.

Predicting the risk of early recurrences for each patient may serve as a basis for individualized approaches to selecting interventional treatment methods and scope, as well as determining the intensity and duration of postoperative antiarrhythmic and anticoagulant therapies. Established predictors of unfavorable outcomes, including early and late recurrences after CA, include factors such as age, obesity, severe cardiovascular pathology, AF type and duration, and significant structural heart alterations [14]. In this study, no significant clinical or demographic differences were observed between groups. However, atrial tachyarrhythmia recurrences were more frequent in patients with persistent AF, regardless of arrhythmia duration.

Patients with arrhythmia recurrences had larger vertical dimensions and LA volumes on Echo and CT, both considered established predictors of CA effectiveness. Interestingly, there were no intergroup differences in anterior-posterior LA size or LA volume index [15].

The pathophysiological basis of atrial remodeling involves myocardial replacement by fibrotic tissue. According to a meta-analysis by Kh. Ghafouri et al. based on 24 studies, the most predictive parameter for CA effectiveness was quantified LA fibrosis from cardiac MRI data: a 10% fibrosis increase was associated with a 1.54-fold higher recurrence rate of AF (95% CI: 1.39-1.70, I^2=50.1%) [18]. Low-amplitude activity zones on intraoperative voltage mapping visualize and quantify fibrotic substrates, with results comparable to cardiac MRI data, as confirmed by a meta-analysis including 22 studies conducted by G.Bijvoet et al.

In this study, the extent of low-amplitude activity zones was categorized based on LA involvement, consistent with domestic and international research [8, 12]. Analysis revealed that low-amplitude activity was more frequent in patients with early recurrences, with greater zone extent emerging as the most significant predictor of early atrial tachyarrhythmia recurrence after CA. Similar findings were reported by E.V. Dedukh et al., where logistic regression analysis identified widespread low-amplitude zones (covering >20% of the LA area, p=0.026) as independent predictors of AF recurrence [12].

Our study focused on atrial deformation parameters, indirectly reflecting myocardial functional status during remodeling. Many researchers have validated the prognostic significance of LA deformation during the reservoir phase [7]. However, few studies, particularly in domestic literature, have assessed the contributions of each LA deformation component (reservoir, conductor, and contractile phases) to CA outcome prediction. Globally, only a few studies, such as that by A.V. Nielsen et al., have an-

Table 3.

Relation of factors to the risk of recurrence of atrial tachyarrhythmias after 3 months

Indicator	Univariate analysis		Multivariate analysis	
	OR; 95% CI	p	OR; 95% CI	p
Persistent form of AF	8.63; 1.88-39.6	0.005	7.47; 1.62-34.4	0.010
LA vertical size (Echo)	1.26; 1.03-1.54	0.012	-	-
RA vertical size (Echo)	1.22; 0.997-1.49	0.53	-	-
LA volume (Echo)	1.46; 1.00- 1.09	0.027	-	-
LA volume without appendage (CT)	1.05; 0.996-1.10	0.037	-	-
LA volume with appendage (CT)	1.06; 1.02-1.11	<0.001	1.05;1.01-1.10	0.017
LA vertical size (CT)	1.09; 1.00-1.19	0.013	1.35; 1.05-1.72	0.018
LA reservoir function	0.747; 0.618-0.904	<0.001	0.772; 0.630-0.943	0.012
LA conductive function	0.838; 0.700-1.00	0.028	-	-
LA stiffness index	1.01; 1.00-1.02;	0.011	-	-
Presence of low-amplitude activity zones	6.81; 1.51-30.6	0.011	-	-
SP of low-amplitude activity zones	2.96; 1.49-5.89	0.001	2.65; 1.21-5.79	0.018

Note: hereinafter, CT - computed tomography; AF - atrial fibrillation; SP - spread percentage

alyzed this aspect. In a cohort of 678 patients with various AF types, LA contractile function was the strongest independent predictor of recurrence after CA (odds ratio 1.07, 95% CI: 1.01-1.12, p=0.012) with a threshold value of 11.1% [16]. In our research, significant predictive value was demonstrated for both the LA reservoir and conductor functions.

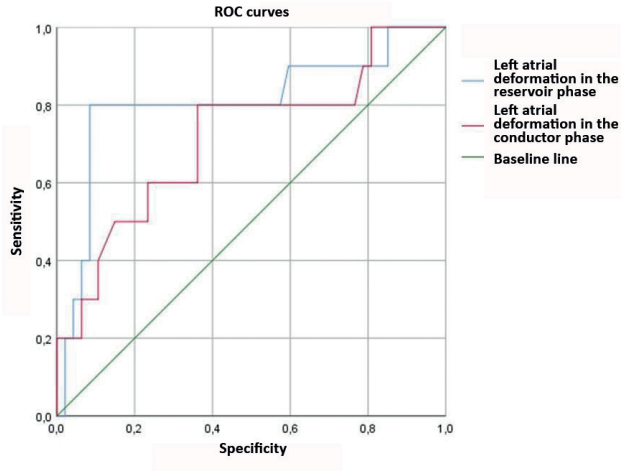

Figure 4. Indicators showing an inverse relationship with the likelihood of early recurrences of atrial tachyarrhythmias after catheter ablation.

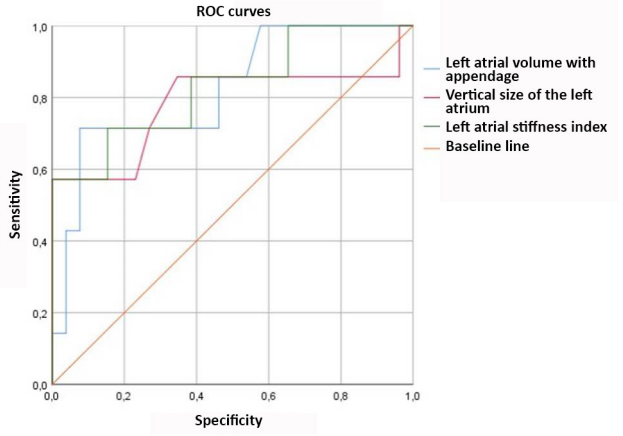

Figure 5. Indicators showing a direct relationship with the likelihood of early recurrences of atrial tachyarrhythmias after catheter ablation.

Our study also demonstrated the high prognostic value of the LA stiffness index, based on longitudinal deformation, reflecting LA rigidity and fibrosis. Similar results were previously reported by I.M. Khurram et al. [17], where patients with long-term atrial tachyarrhythmia recurrences (10.4±7.6 months follow-up) had a higher LA stiffness index (0.83±0.46 vs. 0.40±0.22, p<0.001). However, this index had not been previously evaluated for early recurrences after CA.

Thus, assessing LA deformation and calculating the LA stiffness index preoperatively may allow for a more justified approach to AF treatment strategies and evaluating the need for repeat interventions in cases of early or late atrial tachyarrhythmia recurrences. Given that patients with early recurrences more often exhibited persistent AF and larger low-amplitude activity zones on intraoperative voltage mapping, individualized approaches to arrhythmia substrate modification, expanding LA ablation scope, could be considered for these patients.

Study limitations

The limitations of this study include the small number of patients in the observation groups, the lack of categorization of patients based on the timing of the first atrial tachycardia paroxysm after RFA, and the reliance on interviews and the analysis of submitted ECGs and Holter monitoring data for information on recurrences. The absence of implanted ECG monitoring systems reduces the reliability of the recurrence data.

CONCLUSION

According to our study, early recurrences occurred in 17.5% of patients. A high degree of low-amplitude activity in the LA based on high-density voltage mapping and the presence of persistent AF, regardless of the duration of arrhythmia history, were identified as the strongest independent predictors of early atrial tachyarrhythmia recurrences. A reduction in LA deformation during the reservoir phase below 21.7% and during the conductor phase below 15.7%, an increase in the LA stiffness index above 0.314 relative units, an LA volume with the appendage exceeding 121.7 ml, and an LA vertical size above 65.5 mm on CT imaging predict the risk of early recurrences with high sensitivity and specificity.

REFERENCES

1. Arakelyan MG, Bockeria LA, Vasilieva EYu et al. Clinical guidelines for Atrial fibrillation and atrial flutter. *Russ J Cardiol*. 2021;26(7): 190-260. (In Russ.). https://doi.org/10.15829/1560-4071-2021-4594.

2. Kanorskii SG. Choice of sinus rhythm control strategy in patients with atrial fibrillation: why, when and how?A review. *Journal of Arrhythmology.* 2023.30(111): 52-60.(In Russ.). https://doi.org/10.35336/VA-2023-1-07.

3. Calkins H, Hindricks G, Cappato R, et al. HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10): e275-e444. https://doi.org/10.1016/j.hrthm.2017.05.012.

4. Mohanty S, Mansour M, Natale A. Identifying the prognostic significance of early arrhythmia recurrence during the blanking period: a pursuit to rediscover the past. *Europace.* 2023;25(9): euad229. https://doi.org/10.1093/europace/euad229.

5. Steinberg C, Champagne J, Deyell MW, et al. CIRCA-DOSE Study Investigators. Prevalence and outcome of early recurrence of atrial tachyarrhythmias in the Cryoballoon vs Irrigated Radiofrequency Catheter Ablation (CIRCA-DOSE) study. *Heart Rhythm.* 2021;18(9): 1463-1470. https://doi.org/10.1016/j.hrthm.2021.06.1172.

6. Cau R, Bassareo P, Suri JS, et al. The emerging role of atrial strain assessed by cardiac MRI in different cardiovascular settings: an up-to-date review. *Eur Radiol.* 2022;32(7): 4384-4394. https://doi.org/10.1007/s00330-022-08598-6.

7. Bajraktari G, Bytyci I, Henein MY. Left atrial structure and function predictors of recurrent fibrillation after catheter ablation: a systematic review and meta-analysis. *Clin Physiol Funct Imaging.* 2020;20(1): 1-13. https://doi.org/10.1111/cpf.12595.
8. Masuda M, Fujita M, Iida O, et al. Left atrial low-voltage areas predict atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. *Int J Cardiol.* 2018;15(257): 97-101. https://doi.org/10.1016/j.ijcard.2017.12.089.
9. Junarta J, Siddiqui MU, Riley JM, et al. Low-voltage area substrate modification for atrial fibrillation ablation: a systematic review and meta-analysis of clinical trials. *Europace.* 2022;13(24): 1585-1598. https://doi.org/10.1093/europace/euac089.
10. Arshinova IA, Poltavskaya MG, Sedov VP, et al. Characteristics of left atrial myocardial deformation in patients with atrial fibrillation after. *Medical alphabet.* 2021;39: 20-25. (In Russ.). https://doi.org/10.33667/2078-5631-2021-39-20-25.
11. Badano LP, Kolias TJ. Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19(6): 591-600. https://https://doi.org/10.1093/ehjci/jey042.
12. Dedukh EV, Yashkov MV, Taymasova IA, et al. Algorithm for determining the fibrosis stage using high-density mapping. *Journal of Arrhythmology.* 2022; 29(109): 29-36. (In Russ.). https://doi.org/10.35336/VA-2022-3-04.
13. Revishvili ASh, Bojcov SA, Davtjan KV, et al. Guideline for electrophysiological studies, catheter ablation and the use of implantable antiarrhythmic devices. New edition. 2017; pp. 544-598 (In Russ). ISBN 9785950092206.
14. Mikhaylov EN, Gasimova NZ, Ayvazyan SA, et al. Factors associated with the efficacy of atrial fibrillation radiofrequency catheter ablation: opinion of the specialists who use the "ablation index" module. *Journal of Arrhythmology*. 2020;27(101): 9-24. (In Russ.) https://doi.org/10.35336/VA-2020-3-9-24.
15. Nedios S, Lindemann F, Heijman J, et al. Atrial remodeling and atrial fibrillation recurrence after catheter ablation: Past, present, and future developments. *Herz.* 2021;46(4): 312-317. https://doi.org/10.1007/s00059-021-05050-1.
16. Nielsen AB, Skaarup KG, Djernæs K, et al. Left atrial contractile strain predicts recurrence of atrial tachyarrhythmia after catheter ablation. *International Journal of Cardiology*. 2022;1(358): 51-57. https://doi.org/10.1016/j.ijcard.2022.04.056.
17. Ghafouri K, Franke KB, Foo FS, et al. Clinical utility of cardiac magnetic resonance imaging to assess the left atrium before catheter ablation for atrial fibrillation. A systematic review and meta-analysis. *International Journal of Cardiology.* 2021;15(339): 192-202. https://doi.org/10.1016/j.ijcard.2021.07.030.

https://doi.org/10.35336/VA-1409

RISK STRATIFICATION FOR VENTRICULAR TACHYARRHYTHMIAS AFTER CARDIOVERTER-DEFIBRILLATOR IMPLANTATION FOR PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH: RESULTS OF THE IDEAL SINGLE-CENTER PROSPECTIVE STUDY

N.N.Ilov[1,2], O.V.Palnikova[1,2], D.R.Stompel[1,2], D.A.Zorin[2], E.I.Romantsov[2], M.G.Terent'eva[2], A.M. Abdulkadyurov[2], D.R.Paskeev[2], E.A.Kulikova[2], D.O.Klimchuk[2], O.V.Petrova[1,2], A.A.Nechepurenko[2], V.N.Kolesnikov[2], S.A.Boytsov[3]

[1]FSBEI of HE Astrakhan State Medical University, MH RF, Russia, Astrakhan, 121 Bakinskaya str.; [2]FSBI "Federal Center for Cardiovascular Surgery" of the MH RF, Russia, Astrakhan, 4 Pokrovskaya Roshcha str.; [3]FSBI"NMRC of Cardiology named after acad. E.I.Chazov" of the MH RF, Russia, Moscow, 15A Academician Chazov str.

Aim. The aim of this study was to develop additional selection criteria for implanted cardioverter-defibrillator (ICD) implantation in the primary prevention of sudden cardiac death (SCD) based on the risk stratification for the development of sustained ventricular tachycardia (VT).

Methods. The study included 451 patients with heart failure and reduced left ventricular ejection fraction (HFrEF) who were referred for ICD implantation for primary prevention of SCD. Participants underwent pre-implantation screening of clinical, instrumental, and laboratory parameters, followed by prospective observation for 24 months to record the first occurrence of sustained VT or justified ICD therapy. To achieve the study's goal, training and test samples were formed.

Results. The arrhythmic endpoint was recorded in 84 patients (26%) in the training group and in 35 patients (27%) in the test group. Univariate analysis identified 11 factors with the highest predictive potential ($p<0.1$) associated with the occurrence of the studied endpoint. These included clinical data: coronary artery disease, arterial hypertension, resting heart rate >80 bpm; electrocardiographic parameters: complete left bundle branch block according to Strauss criteria, P-wave duration (lead II) >120 ms, or the presence of atrial fibrillation (in the case of persistent form), index of cardiac electrophysiological balance (ICEB) >3.1; echocardiographic parameters: presence of eccentric left ventricular hypertrophy, global longitudinal strain ≥ minus 6%; laboratory markers: galectin-3 >12 ng/ml, sST-2 >35 ng/ml, NT-proBNP >2000 pg/ml. Based on the regression coefficients, points were assigned to each factor, and the sum of these points determined the value of a new proposed index - the arrhythmic risk index (ARI). ARI values >5 points predicted the two-year likelihood of VT in HFrEF patients with a sensitivity of 78.6% and specificity of 64.3% (AUC=0.788±0.028 with 95% confidence interval (CI): 0.732-0.843; p=0.0001). The application of ARI in the test group demonstrated good model performance in predicting two-year VT risk (AUC=0.652±0.053 with 95% CI: 0.547-0.757; p=0.008).

Conclusion. Based on the obtained results, a predictive index was developed, allowing for personalized and timely risk assessment of VT in patients with HFrEF.

Key words: chronic heart failure; prediction; ventricular tachyarrhythmias; sudden cardiac death; implantable cardioverter-defibrillators

Conflict of Interest: none.
Funding: none.
Received: 25.08.2024 **Revision received:** 01.11.2024 **Accepted:** 28.11.2024
Corresponding author: Ilov Nikolay, E-mail: nikolay.ilov@gmail.com

N.N.Ilov - ORCID ID 0000-0003-1294-9646, O.V.Palnikova - ORCID ID 0000-0002-4476-5174, D.R.Stompel - ORCID ID 0000-0002-2400-8045, D.A.Zorin - ORCID ID 0000-0001-7167-4713, E.I.Romantsov - ORCID ID 0000-0002-8153-6637, M.G.Terent'eva - ORCID ID 0000-0001-6075-3133, A.M.Abdulkadyurov - ORCID ID 0000-0003-3984-1678, E.A.Kulikova - ORCID ID 0009-0000-9726-0412, D.O.Klimchuk - ORCID ID 0000-0003-1848-216X, O.V.Petrova - ORCID ID 0000-0003-3544-2266, A.A.Nechepurenko - ORCID ID 0000-0001-5722-9883, V.N.Kolesnikov - ORCID ID 0009-0003-0637-1427, S.A.Boytsov- ORCID ID 0000-0001-6998-8406

For citation: Ilov NN, Palnikova OV, Stompel DR, Zorin DA, Romantsov EI, Terent'eva MG, Abdulkadyurovв AM, Paskeev DR, Kulikova EA, Klimchuk DO, Petrova OV, Nechepurenko AA, Kolesnikov VN. Risk stratification for ventricular tachyarrhythmias after cardioverter-defibrillator implantation for primary prevention of sudden cardiac death: results of the IDEAL single-center prospective study. *Journal of Arrhythmology.* 2024;31(4): 47-58. https://doi.org/10.35336/VA-1409.

Sudden cardiac death (SCD), alongside critical cardiac decompensation, is a leading cause of cardiovascular mortality in patients with heart failure with reduced ejection fraction (HFrEF) of the left ventricle (LV). SCD is defined as natural death due to cardiac pathology, preceded by sudden loss of consciousness within one hour of the onset of acute symptoms, where prior heart disease may be known but the occurrence of death is unexpected

[1]. The term “sudden cardiac death” is based on a specific mechanism of death rather than a specific cause. In the vast majority of cases, the mechanism of circulatory arrest is ventricular tachyarrhythmias (VT) [2].

The predominantly arrhythmogenic nature of SCD forms the basis for its prevention using implantable cardioverter-defibrillators (ICDs). Today, ICDs should be regarded as the primary tool for both primary and secondary prevention of SCD, with a strong evidence base and high-level indications [3, 4]. Randomized controlled trials have demonstrated the effectiveness of ICDs in the primary prevention of SCD in patients with chronic heart failure (CHF) and an LV ejection fraction (LVEF) ≤35% [5, 6].

However, many experts believe that determining indications for interventional primary prevention of SCD solely based on LVEF requires reconsideration. Consequently, the search for new predictors to identify very high-risk groups for SCD among HFrEF patients is considered a pressing and necessary task. Currently, diagnostic tools aimed at identifying potential morphological and electrophysiological substrates required for the realization of the arrhythmogenic SCD scenario are seen as the most promising [7]. The presence of such arrhythmogenic potential can be inferred from prolonged or shortened corrected QT interval (QTcor) on electrocardiograms, changes in the interval from the peak to the end of the T wave (TpTe) [8, 9], and voltage criteria for LV hypertrophy (LVH) [10]. A simple, non-invasive method for diagnosing and monitoring myocardial fibrosis is the measurement of circulating profibrogenic biological agents in the blood, which may serve as indicators of risk for adverse clinical events, including SCD [11].

Risk stratification for fatal ventricular arrhythmias can also be aided by transthoracic echocardiographic (EchoCG) parameters [12], two-dimensional myocardial strain imaging [13], and myocardial contrast imaging with gadolinium chelates during cardiac magnetic resonance imaging (MRI) [14]

A multifactorial approach to VT risk assessment has been advocated. H.T. Reeder et al., based on secondary analysis of data from the SCD HEFT (Sudden Cardiac Death in Heart Failure Trial), proposed a regression model for predicting ICD-delivered electrical therapy, which included atrial fibrillation (AF), diabetes mellitus, coronary artery disease (CAD), blood creatinine and sodium levels, age, CHF functional class, and LVEF [15]. J. Lupon et al. included age, gender, LVEF, CHF duration, and biochemical markers (eGFR and ST2) in their predictive model for estimating the five-year risk of SCD [16]. The intensity of gadolinium uptake on cardiac MRI, age, history of syncope, AF/flutter, nonsustained VT, and AV block formed the basis of the ESTIMATED index developed by Chinese researchers for VT risk stratification in patients with non-ischemic CHF [17]. However, even such a comprehensive approach has not led to a significant improvement in VT risk stratification in HFrEF patients, highlighting the need for continued research in this area.

Aim of the study: to develop additional selection criteria for ICD implantation for the primary prevention of SCD based on risk stratification for sustained VT.

METHODS

The data presented in this article were obtained from the completed single-center prospective IDEAL study. The detailed study design is available in the public registry at clinicaltrials.gov (NCT05539898). Inclusion criteria were the current indications for ICD implantation for primary prevention of SCD [2]: CHF of NYHA functional class II-III with an LVEF ≤35% on optimal medical therapy for at least six months. Mandatory inclusion criteria included the completion of maximal myocardial revascularization (if indicated).

Exclusion criteria: Hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, confirmed hereditary channelopathies, indications for cardiac surgery (revascularization, valve insufficiency correction), documented sustained VT episodes, family history of SCD, history of syncope, or previous SCD episodes [18].

The study design is shown in Figure 1. Patient selection was conducted between 2012 and 2021. After evaluating inclusion and exclusion criteria, a standard clinical examination was performed according to the CHF diagnostic algorithm. Additional assessments included speckle-tracking EchoCG and blood biomarker measurements (electrolytes, C-reactive protein, creatinine, soluble suppressor of tumorigenesis-2 [sST-2], NT-proBNP, galectin-3). Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) based on serum creatinine levels.

All included patients received dual-chamber ICDs or ICDs with cardiac resynchronization therapy (CRT-D) as a means of primary SCD prevention. Participants were prospectively observed for 24 months post-ICD implantation

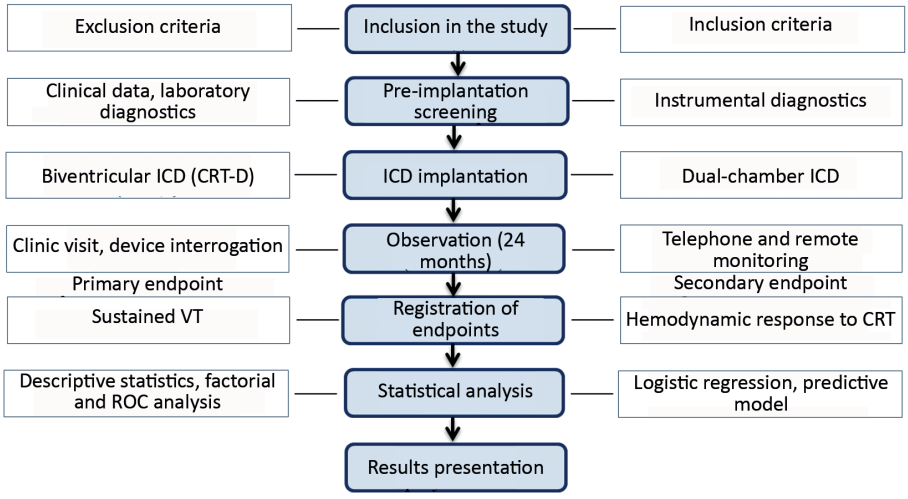

Figure 1. Flow chart illustrating the study design. Abbreviations: VT - ventricular tachyarrhythmia; ICD - implantable cardioverter-defibrillator; CRT-D - implantable cardioverter-defibrillator with cardiac resynchronisation therapy function.

by cardiologists at their local facilities and at the implanting center. This follow-up ensured proper monitoring of medical therapy and the registration of study endpoints.

The primary endpoint was the first occurrence of a sustained VT episode (≥30 seconds), detected in the VT "monitor" zone or requiring electrical therapy (antitachycardia pacing or shock therapy) during the two-year observation period. Hemodynamic response to CRT was also evaluated. According to previous findings, an LVEF improvement of ≥5% is sensitive to arrhythmic risk modification [8]. The same approach was applied to assess CRT response concerning the study endpoint.

Statistical Analysis

Subsequent statistical analysis was performed using methods aligned with the study's objectives. The research methods, including statistical techniques, have been described in earlier publications [19-21]. IBM SPSS Statistics 26 and Jamovi 2.3.28 software were used for generat-

Table 1.

Comparative characteristics of patients in the training and test cohorts

Clinical indicator	Training cohort (n=319)	Test cohort (n=132)	p
Age, years	57 (51-63)	57 (52-61)	0.557
Male sex, n (%)	265 (83)	106 (80)	0.484
Body mass index, kg/m^2	28.7 (25.4-32.5)	29.3 (25.7-32.7)	0.646
Coronary artery disease, n (%)	160 (50)	59 (45)	0.291
Post-infarction cardiosclerosis*, n (%)	118 (37)	44 (34)	0.480
Non-ischaemic cardiomyopathy, n (%)	159 (50)	73 (55)	0.291
Coronary artery lesions#, n (%)	132 (41)	65 (49)	0.126
Chronic heart failure II FC, n (%)	22 (7)	5 (4)	0.201
Chronic heart failure III FC, n (%)	233 (74)	95 (72)	0.739
History of arterial hypertension, n (%)	180 (56)	69 (52)	0.420
Diabetes mellitus, n (%)	61 (19)	26 (20)	0.888
History of obesity	119 (37)	46 (35)	0.622
Stroke, n (%)	20 (6)	11 (8)	0.431
Chronic kidney disease, n (%)	139 (46)	50 (41)	0.379
AF (paroxysmal/persistent), n (%)	90 (28)	41 (31)	0.544
AF (permanent), n (%)	26 (8)	9 (7)	0.618
History of non-sustained ventricular tachycardia, n (%)	43 (13)	10 (8)	0.076
Systolic blood pressure, mmHg	120 (110-130)	120 (110-130)	0.294
Diastolic blood pressure, mmHg	80 (70-80)	80 (70-80)	0.289
Heart rate, bpm	78 (68-90)	78 (68-88)	0.976
NT-proBNP, pg/ml	2446 (1350-5049)	2683 (1409-4958)	0.782
Glomerular filtration rate (CKD EPI), ml/min/1.73 m^2	67 (58-77)	67 (63-76)	0.092
Cardiac surgeries			
Revascularisation&, n (%)	134 (42)	50 (38)	0.361
Valve insufficiency correction, n (%)	62 (20)	25 (19)	0.856
Left ventricular repair, n (%)	29 (9)	8 (6)	0.271
Echocardiographic indicators			
Left ventricular end-diastolic volume, ml	230 (198-288)	223 (182-280)	0.339
Left ventricular end-systolic volume, ml	162 (135-204)	158 (131-198)	0.431
Left ventricular end-diastolic dimension, cm	6.7 (6.3-7.4)	6.6 (6.1-7.2)	0.250
Left ventricular end-systolic dimension, mm	5.8 (5.2-6.5)	5.6 (5.1-6.3)	0.481
Left ventricular ejection fraction (Simpson), %	29 (24-33)	29 (25-34)	0.355
Implanted cardioverter-defibrillator			
Cardioverter-defibrillator with CRT function, n (%)	190 (60)	78 (59)	0.926
Dual-chamber cardioverter-defibrillator, n (%)	129 (40)	54 (41)	0.926

Note: hereinafter, * - among patients with coronary artery disease; # in patients with non-ischaemic cardiomyopathy; FC - functional class; AF - atrial fibrillation; & - coronary artery bypass grafting or percutaneous coronary intervention; CRT - cardiac resynchronisation therapy.

ing graphs and charts to illustrate results. Data in tables are presented as absolute patient counts (%) or as Me (Q1-Q3), unless otherwise stated.

Sample size calculations for statistically significant results in logistic regression were performed using GPower 3.1.9.4 software with a priori power calculation for z-tests. Input parameters included two-sided asymptotic significance, $\alpha = 0.05$, $\beta = 20\%$, yielding a study power of 80%, binomial distribution, balanced model ($\pi = 0.5$), and a correction for interaction among independent factors of 0.1 (for R^2). Sample size calculations assessed the impact of each predictor on outcomes. The odds of the outcome occurring in the study group were 2.5 times higher than in the control group for the predictor "Presence of coronary artery disease" (odds ratio [OR] 2.2; 95% confidence interval [CI]: 1.2-5.1) [22]. With these parameters, the sample size required was 214 participants. To achieve the study's objectives, a total of at least 450 patients were planned to be included, divided into two groups: training and testing cohorts.

RESULTS

Clinical and demographic characteristics of patients undergoing prospective observation

After screening for inclusion and exclusion criteria, 539 patients were enrolled in the study. During the two-year follow-up, 88 patients were excluded for various reasons (loss of contact - 71 patients, non-cardiac deaths - 12 patients, and heart transplantation - 5 patients). The final cohort included 451 CHF patients with NYHA class II-III and an LVEF of 29 (25-33)%. The majority of patients were male (371 patients, 82%) of working age - 57 (51-62) years.

Before study enrollment, patients underwent maximal possible myocardial revascularization (184 patients, 41%), and valve pathology correction was performed if indicated (87 patients, 19%). All patients received optimal medical therapy for CHF in accordance with current clinical guidelines at the time of inclusion. During prospective follow-up, medical therapy was adjusted based on clinical status and opportunities to introduce new CHF medications. Quadritherapy, as per the 2020 CHF treatment recommendations, was prioritised [23].

At the end of the follow-up period, patients were divided into two groups: a training sample, used to identify prognostic factors and develop multifactorial prognostic models, and a test sample, used to validate the accuracy of predictions for the studied endpoints. Groups were formed through random selection in a 70:30 ratio. These groups did not differ significantly in key clinical-demographic parameters or known risk factors for the studied endpoints (Tables 1 and 2).

Incidence of the primary endpoint and clinical predictors of VT

During the two-year follow-up, the arrhythmic endpoint was observed in 84 patients (26%). Groups were comparable in most clinical-demographic characteristics based on endpoint achievement.

Coronary artery disease (CAD) with stenosis >30% was an important prognostic factor for VT in both non-ischemic cardiomyopathy (NICM) (OR 3.23; 95% CI: 0.99-10.54; p=0.052) and ischemic cardiomyopathy (ICM) (OR 4.61; 95% CI: 1.44-14.79; p=0.010). Kaplan-Meier survival analysis showed earlier clinically significant first VT episodes in CAD patients. Median freedom from VT was 19.7 (95% CI: 18.6-20.9) months in CAD patients and 21.6 (95% CI: 20.8-22.5) months in NICM patients (p=0.036).

Electrocardiographic Predictors of VT

Before ICD implantation, most patients had sinus rhythm (81%). The cohort was characterised by leftward electrical axis deviation (71%), voltage signs of LVH (62%), interatrial conduction disturbances (P-wave duration - 120 [101-120] ms), and prolonged ventricular electrical systole (QTcor - 465 [438-498] ms).

Patients without VT had longer QRS durations (p=0.01) and more frequent complete left bundle branch block (LBBB) (p=0.004). VT patients showed a higher index of cardiac electrophysiological balance (ICEB) (p=0.033). An ICEB cutoff >3.1 correlated with increased VT risk (OR 1.67; 95% CI: 1.01-2.76; p=0.044). P-wave durations >120 ms doubled VT risk (OR 2.10; 95% CI: 1.09-4.07; p=0.026).

Echocardiographic Predictors of VT

Both groups exhibited significant increases in the linear and volumetric dimensions of the LV and reductions in LVEF. The echocardiographic parameters indicated pathological LV remodeling, predominantly of the eccentric hypertrophy type (78%). Patients free of VT were more likely to have LV remodeling consistent with eccentric hypertrophy (83% vs. 66%; p=0.002), whereas patients with VT more frequently exhibited concentric LV hypertrophy (13% vs. 6%; p=0.053) with increased posterior wall thickness (p=0.016).

In all patients who underwent speckle-tracking echocardiography (n=133), significant shifts in longitudinal strain parameters were detected across most LV myocardial segments. Comparative analysis of peak systolic longitudinal strain values revealed worse deformation characteristics in the LV segments corresponding to the inferior and anterior walls in VT patients (p=0.001) (Figure 2).

Table 2.

Medication therapy in patients from the training and test cohort

	Training cohort (n=319)	Test cohort (n=132)	p
β-blockers, n (%)	451 (100)	451 (100)	-
ACEI/ ARB, n (%)	218 (68)	87 (66)	0.616
ARNI, n (%)	111 (35)	43 (33)	0.651
MRA, n (%)	283 (89)	114 (86)	0.484
Loop diuretics, n (%)	311 (98)	125 (95)	0.132
SGLT2 inhibitors, n (%)	52 (16)	21 (16)	0.918
Amiodarone, n (%)	123 (39)	51 (39)	0.717

Note: hereinafter, ACEI - angiotensin-converting enzyme inhibitors; ARNI - angiotensin receptor-neprilysin inhibitors; MRA - mineralocorticoid receptor antagonists; ARB - angiotensin receptor blockers; SGLT2 - sodium-glucose cotransporter 2.

The arrhythmic endpoint was directly associated with global longitudinal strain (GLS): VT patients demonstrated lower absolute GLS values, indicative of worse longitudinal LV deformation. ROC analysis was performed to determine the critical GLS cutoff value. The area under the ROC curve (AUC) was 0.664 ± 0.061 (95% CI: 0.544-0.783). A GLS cutoff of -6% predicted the first VT manifestation with 44% sensitivity and 76% specificity. It was found that GLS values <-6% increased the risk of the first VT manifestation during the observation period by almost threefold (OR 2.59; 95% CI: 1.07-6.26; p=0.031). Differences in global circumferential strain values were close to significance (p=0.055).

Using the same cutoff value (<-6%) for regional strains, it was observed that impaired longitudinal deformation in the anterior segments increased VT risk by 3.5 times (OR 3.57; 95% CI: 1.40-9.09; p=0.006), while impairment in the inferior segments increased the risk nearly eightfold (OR 7.67; 95% CI: 2.75-21.38; p=0.0001).

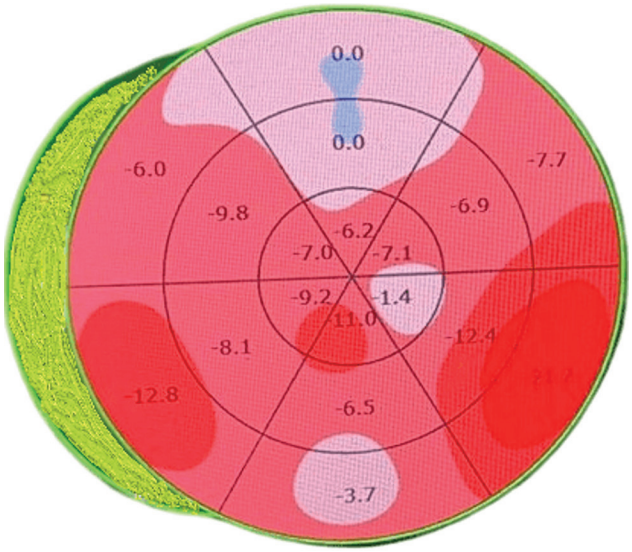

Figure 2. Distribution pattern of regional longitudinal strain on the 18-segment left ventricular model («bull's eye») before ICD implantation in a patient with ventricular tachycardia registered during follow-up. Amidst diffuse longitudinal strain reduction, the poorest myocardial longitudinal strain parameters of the left ventricle were observed in the anterior and inferior segments.

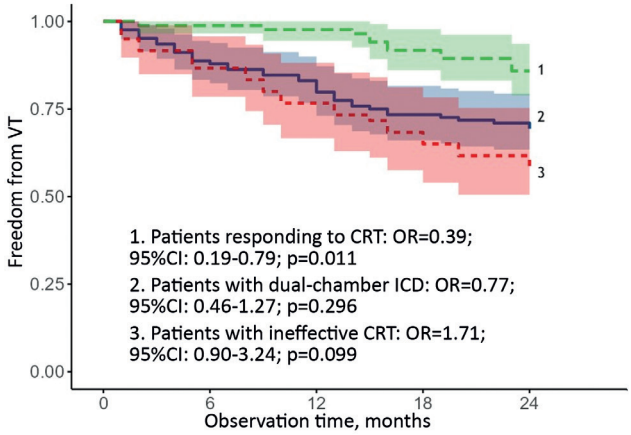

Figure 3. Kaplan-Meier curve illustrating the incidence of the arrhythmic endpoint depending on the application and effectiveness of cardiac resynchronisation therapy (CRT). Abbreviations: VT - ventricular tachyarrhythmia; ICD - implantable cardioverter-defibrillator; CRT - cardiac resynchronisation therapy.

Biomarkers Indicating VT Risk

Analysis of blood biomarkers revealed significant differences in NT-proBNP and sST-2 concentrations (p=0.001 and p=0.021, respectively). The difference in galectin-3 levels was close to statistical significance (p=0.066). ROC analysis was performed to determine critical thresholds for these quantitative predictors (p<0.05). It was found that sST-2 >35 ng/mL increased the risk of the first VT manifestation during the observation period nearly threefold (OR 2.86; 95% CI: 1.23-6.64; p=0.013). Similarly, galectin-3 >12 ng/mL had comparable prognostic significance (OR 2.64; 95% CI: 1.06-6.53; p=0.032). Conversely, NT-proBNP >2000 pg/mL was associated with a 2.2-fold lower risk for the same outcome (OR 0.46; 95% CI: 0.22-0.95; p=0.034). In groups with elevated levels of these biomarkers, the median time to VT was earlier: 18.7 (0.8) months (95% CI: 19.8-22.8 months) for sST-2 >35 ng/mL and 19.1 (0.9) months (95% CI: 17.4-20.8 months) for galectin-3 >12 ng/mL.

Effect of CRT on VT Risk

In the CRT-D group, CRT was effective in 112 patients (59%), with LVEF improving from 27 (22-32)% to 39 (34-45)% (p=0.0001). Absolute LVEF improvement was as follows: ≤35% in 45 patients (40%), 36-40% in 21 patients (19%), and >40% in 46 patients (41%). VT incidence was significantly lower in patients who responded to CRT (14% vs. 42% in the non-responders). The impact of effective CRT on arrhythmic risk was further supported by survival analysis (Figure 3).

The data demonstrated that an LVEF increase of ≥5% reduced VT risk fourfold (OR 0.23; 95% CI: 0.10-0.51; p=0.0001). A more pronounced hemodynamic response to CRT was observed in patients without VT. However, CRT alone, without consideration of its effectiveness, did not show a significant impact on arrhythmic endpoints (OR 0.77; 95% CI: 0.46-1.27; p=0.296).

Multivariate Analysis of VT Predictors and Prognostic Models

Univariate analysis identified 11 factors with high predictive potential (p<0.1) related to the primary endpoint. Based on these factors, binary logistic regression was used to develop prognostic models for predicting the two-year likelihood of VT in HFrEF patients. The best regression model (Table 3), with optimal sensitivity and specificity, was statistically significant (p=0.001). The Nagelkerke coefficient of determination indicated that 32.1% of the variance in VT probability was explained by the studied factors.

Diagnostic performance, at a regression function cutoff of 0.257, was 74.6% (sensitivity - 74.7%; specificity - 74.5%). The area under the ROC curve (AUC) for the two-year VT prediction was 0.802, indicating excellent model quality.

Most parameters showed a direct relationship with VT probability, except "presence of LBBB per Strauss criteria," "eccentric LV hypertrophy," and "NT-proBNP >2000 pg/mL," which had an inverse relationship. Based

on calculated β-coefficients, scores were assigned to each factor, and their sum determined a new proposed index-the Arrhythmic Risk Index (ARI) (Table 4). ROC analysis established a threshold value of 5 points for ARI. ARI >5 points predicted the two-year VT probability in HFrEF patients with a sensitivity of 78.6% and specificity of 64.3% (AUC=0.788 ± 0.028; 95% CI: 0.732-0.843; p=0.0001).

Validation in Test Cohort

Applying ARI in the test cohort demonstrated good model performance for predicting two-year VT risk (AUC=0.652 ± 0.053; 95% CI: 0.547-0.757; p=0.008). Each 1-point increase in ARI raised VT risk by 1.08 times (95% CI: 1.02-1.15; p=0.015). ARI >5 points increased the two-year VT risk fourfold (OR 4.04; 95% CI: 1.77-9.24; p=0.001) with 68.6% sensitivity and 64.9% specificity. Among high-risk VT patients (ARI >5 points, n=58), the arrhythmic endpoint was observed in 41% (24 patients) during the two-year follow-up, compared to 15% (11 patients) in the low-risk group (ARI ≤5 points, n=74) (Figure 4).

DISCUSSION

During the two-year observation period, the arrhythmic endpoint was registered in 84 patients (26%). Overall, many experts have noted a global trend of decreasing ICD electrical therapy activation rates [24]. This trend can be attributed to two main factors. First, the evolution of device programming strategies, including prolonged episode detection durations and higher detection thresholds for VT zones requiring active electrical therapy. Second, changes in the clinical profiles of HFrEF patients due to advancements in pharmacological and interventional cardiovascular therapies, as well as improved preventive measures. Consequently, the applicability of findings from earlier studies may need reevaluation, and the prediction of adverse outcomes, including VT risk, should rely on data derived from contemporary HFrEF cohorts.

The limitations of the current SCD risk stratification system, which is based solely on LVEF, are highlighted by several studies. For example, the DANISH trial demonstrated that ICD implantation for primary prevention of SCD in patients with symptomatic CHF of non-ischemic origin did not reduce mortality in those receiving modern CHF therapy [25]. As a result, ICDs are not always implanted in patients with the most urgent need. Additionally, the high cost of this procedure and the necessity for device replacement (reimplantation) every 4-5 years, accompanied by risks such as system infections and infective endocarditis, underscore the need for improved selection criteria for ICD implantation. The most likely solution to this problem is supplementing the current single-factor SCD risk stratification system with new VT predictors [26] and developing effective multifactorial prognostic systems to predict the risk of the first VT episode in HFrEF patients.

Together with this, it would be incorrect to claim that efforts to develop such systems have not been made earlier. For instance, X. Li et al. proposed assessing ICD utility based on VT risk stratification in NICM patients using the ESTIMATED scale (LGE-Based Prediction of SCD Risk in Nonischemic Dilated Cardiomyopathy), which involves quantifying gadolinium accumulation in the myocardium during cardiac MRI [17].

The Seattle Heart Failure Model (SHFM), a prognostic calculator for predicting CHF survival, also deserves mention [27]. The SHFM-D modification (D - Differentiated ICD Benefit), supplemented with data on digoxin and carvedilol use and serum creatinine levels, was designed to stratify patients by the anticipated benefit from ICD implantation [28]. However, it is important to note that SHFM was developed and validated using data from ambulatory patients. Its applicability to hospitalized patients with severe comorbidities (e.g., liver cirrhosis, renal failure, dementia, or cancer) remains questionable.

The MUSIC scale (MUerte Subita en Insuficiencia Cardiaca) allows risk estimation for all-cause mortality, cardiovascular mortality, and SCD based on individual predictors [29]. Notably, some predictors proposed by R. Vazquez et al.-such as AF, CLBBB, and NT-proBNP

Table 3.

Proposed predictors of ventricular tachyarrhythmias

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Clinical predictors						
Presence of CA lesions	3.50	1.20-14.96	0.044	4.59	1.04-34.71	0.078
History of AH	1.56	0.94-2.63	0.092	1.61	0.84-3.13	0.155
HR >80 bpm	1.75	1.05-2.90	0.030	1.65	0.88-3.09	0.117
Electrocardiographic predictors						
P-wave duration >120 ms*	2.96	1.59-5.48	0.001	3.15	1.43-7.06	0.005
CLBBB by Strauss	0.43	0.24-0.76	0.004	0.57	0.23-1.37	0.208
ICEB >3.1	2.01	1.22-3.34	0.007	1.31	0.59-3.00	0.512
Echocardiographic predictors						
Eccentric LVH	0.42	0.23-0.77	0.005	0.26	0.13-0.53	0.001
GLS value <6%	3.06	1.48-6.29	0.002	2.03	0.78-5.20	0.141
Laboratory Ppedictors						
Galectin-3 >12 ng/mL	2.70	1.29-6.39	0.014	3.06	1.20-9.15	0.029
sST-2 >35 ng/mL	3.24	1.78-5.89	0.001	2.44	1.16-5.13	0.018
NT-proBNP >2000 pg/mL	0.28	0.15-0.54	0.001	0.27	0.12-0.58	0.001

Note: hereinafter, OR - odds ratio; CI - confidence interval; CA - coronary arteries; AH - arterial hypertension; HR - heart rate; * - in lead II or permanent atrial fibrillation; CLBBB - complete left bundle branch block; ICEB - index of cardiac electrophysiological balance; LVH - left ventricular hypertrophy; GLS - global longitudinal strain; sST-2 - soluble isoform of tumour suppressor-2; NT-proBNP - N-terminal pro-brain natriuretic peptide.

>1000 pg/mL-are also included in the prognostic scales developed in this study.

Findings from external validation of the MAGGIC scale (The Meta-Analysis Global Group in Chronic Heart Failure) in a retrospective study by M. Canera et al. (1,089 HFrEF patients with ICDs) showed low prognostic accuracy for SCD risk, defined either as any ICD therapy (AUC=0.53; 95% CI: 0.49-0.57) or as a VT episode requiring appropriate shock therapy (AUC=0.52; 95% CI: 0.45-0.59).

L. Shen et al., based on large trials such as PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure), developed predictive models that showed good potential for SCD risk assessment (AUC=0.68) [30]. The authors highlighted two key predictors: NT-proBNP concentration and CHF functional class, both significantly influencing adverse outcome probability. Interestingly, prolonged QRS duration was an SCD marker (OR=1.07; 95% CI: 1.03-1.11 per 5 ms above 120 ms). This finding, however, contrasts with results from this study, likely due to low CRT use among the studied patients (CLBBB prevalence in PARADIGM-HF: 20.1%; in ATMOSPHERE: 21.1%; CRT devices implanted in PARADIGM-HF: 1.9%; in ATMOSPHERE: 1.8%).

In 2020, U.S. researchers developed the MADIT-ICD Benefit Score calculator using clinical data and endpoint information from four MADIT studies-MADIT-2 [5], MADIT-CRT [31], MADIT-RIT [32], and MADIT-RISK-with over 4,500 CHF patients [33]. Accounting for VT or nonarrhythmic death probability, the calculator provides information on ICD benefit levels. Results from ROC analysis after external validation indicated additional prognostic value (C-statistic for VT prediction: 0.75; for nonarrhythmic death prediction: 0.67). However, the calculator was developed using MADIT data collected between 2002 and 2012, and external validation was based on the RAID study, completed in 2017 [34]. Advances in optimal medical therapy since then may limit the MADIT-ICD Benefit Score's effectiveness for CHF outcome prediction [35].

Table 4.

Results of binary logistic regression for predicting the occurrence of VT with conversion of the obtained β-coefficients into scores

Predictor	β-coefficient	Points
Presence of CA lesions	1.523	6
History of AH	0.473	2
HR >80 bpm	0.499	2
P-wave duration >120 ms*	1.147	4
CLBBB by Strauss	-0.566	-2
ICEB >3.1	0.271	1
Presence of ecentric LVH	-1.338	-5
Absolute GLS value <6%	0.707	3
Galectin-3 >12 ng/mL	1.118	4
sST-2 >35 ng/mL	0.890	3
NT-proBNP >2000 pg/mL	-1.319	-5

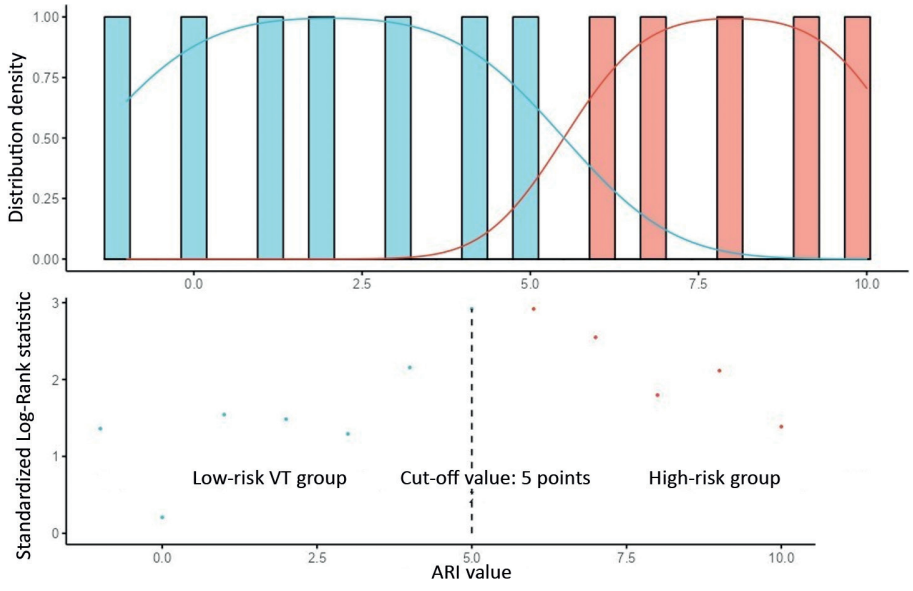

Figure 4. Risk stratification for ventricular tachyarrhythmias (VT) in the test cohort based on the arrhythmic risk index (ARI) values.

The need for external validation of proposed multifactorial prognostic systems across diverse cohorts and ethnic groups cannot be overstated. Despite high diagnostic potential described in original studies, no known prognostic algorithm has yet been incorporated into CHF care standards [23]. This highlights the clinical and economic relevance of improving patient selection criteria for ICD implantation.

Thus, despite substantial clinical material underpinning these conclusions, practical applicability remains uncertain. A key advantage of the prognostic index proposed in this study is its use of well-established clinical factors (e.g., a history of hypertension, coronary artery disease, resting heart rate values) and advanced diagnostics. These include assessments of contemporary blood biomarkers (sST-2, galectin-3), individual electrophysiological status (e.g., intraventricular and atrial conduction disturbances, ICEB), and myocardial deformation properties at both regional and global levels.

Study limitations

A limitation of this study is its single-centre design. The results indicate a lower rate of CRT responders compared to other researchers' findings. It should be emphasised that patient recruitment began in 2012, meaning CRT response may not have been achieved in some cases due to various objective factors, including suboptimal delivery systems, the absence of quadripolar electrodes for

LV pacing, and programming limitations of the implanted devices. The registration frequency of the endpoints might also have been influenced by the introduction of new CHF therapies with antiarrhythmic effects.

Considering the extended follow-up period and the absence of strict monitoring tasks for the prescribed therapies or their impact on endpoints, it is impossible to determine how many patients received CHF quadruple therapy and at what stage of prospective observation. While the lack of quadruple therapy in all patients represents a limitation of the study, it also reflects real-world clinical practice, where the full implementation of CHF quadruple therapy is often unattainable, particularly due to severe arterial hypotension.

CONCLUSION

The study demonstrated the potential for personalised risk assessment of VT. The strategic significance of the proposed multi-marker index lies in its applicability both under comprehensive evaluation of all specified predictors and in settings with limited diagnostic resources, which is particularly relevant for regional healthcare systems.

An important conclusion of the study is the evidence that patients with HFrEF, who have the same class of indication for ICD implantation for primary prevention of SCD according to current clinical guidelines, differ in their arrhythmic risk. This distinction must be considered when developing personalised management strategies for patients with HFrEF.

REFERENCES

1. Revishvili ASh, Rzaev FG, Gorev MV, et al. Klinicheskie rekomendacii. Diagnostika i lechenie fibrilljacii predserdij. 2017. (In Russ.).
2. Nacional`ny`e rekomendacii po opredeleniyu riska i profilaktike vnezapnoj serdechnoj smerti (2-e izdanie). Pod red. Shlyaxto EV, Arutyunova GP, Belenkova YuN, et al. Moscow: Izdatel`skij dom «MeDpraktIka-M», 2018 (In Russ.).
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42: 3599-726. https://doi.org/10.1093/eurheartj/ehab368.
4. Lebedev DS, Mikhailov EN, Neminuschiy NM, et al. Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. *Russian Journal of Cardiology.* 2021;26(7): 4600. (In Russ.)]. doi:10.15829/1560-4071-2021-4600.
5. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *N Engl J Med.* 2002;346: 877-83. https://doi.org/10.1056/NEJMoa013474.
6. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure. *N Engl J Med*. 2005;352:225-37. https://doi.org/10.1056/NEJMoa043399.
7. Masarone D, Limongelli G, Ammendola E, et al. Risk stratification of sudden cardiac death in patients with heart failure: an update. *J Clin Med*. 2018;7: 436. https://doi.org/10.3390/jcm7110436.
8. Ramalho D, Freitas J. Drug-induced life-threatening arrhythmias and sudden cardiac death: A clinical perspective of long QT, short QT and Brugada syndromes. *Rev Port Cardiol.* (English Ed 2018;37: 435-46. https://doi.org/10.1016/j.repce.2017.07.010.
9. Tse G, Gong M, Wong WT, et al. The Tpeak − Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Hear Rhythm.* 2017;14: 1131-7. https://doi.org/10.1016/j.hrthm.2017.05.031.
10. Porthan K, Kenttä T, Niiranen TJ, et al. ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death. *Int J Cardiol.* 2019;276:125-9. https://doi.org/10.1016/j.ijcard.2018.09.104.
11. Ferreira JM, Ferreira SM, Ferreira MJ, et al. Circulating Biomarkers of Collagen Metabolism and Prognosis of Heart Failure with Reduced or Mid-Range Ejection Fraction. *Curr Pharm Des.* 2017;23. https://doi.org/10.2174/1381612823666170317124125.
12. Konety SH, Koene RJ, Norby FL, et al. Echocardiographic predictors of sudden cardiac death. *Circ Cardiovasc Imaging.* 2016;9. https://doi.org/10.1161/CIRCIMAGING.115.004431.
13. Nguyen BL, Capotosto L, Persi A, et al. Global and regional left ventricular strain indices in post-myocardial infarction patients with ventricular arrhythmias and moderately abnormal ejection fraction. *Ultrasound Med Biol.* 2015;41: 407-17. https://doi.org/10.1016/j.ultrasmedbio.2014.09.025.
14. Bazylev VV, Ushakov RYu, Durmanov SS, et al. Prognostic value of delayed gadolinium enhancement on cardiac magnetic resonance imaging in patients with ischemic cardiomyopathy and an implanted cardioverter-defibrillator. *Journal of Arrhythmology.* 2024;31(2): 35-43. (In Russ.). https://doi.org/10.35336/VA-1260.
15. Reeder HT, Shen C, Buxton AE, et al. Joint Shock/Death Risk Prediction Model for Patients Considering Implantable Cardioverter-Defibrillators. *Circ Cardiovasc Qual Outcomes.* 2019;12. https://doi.org/10.1161/CIRCOUTCOMES.119.005675.
16. Lupón J, Cediel G, Moliner P, et al. A bio-clinical approach for prediction of sudden cardiac death in outpatients with heart failure: The ST2-SCD score. *Int J Cardiol.* 2019;293: 148-52. https://doi.org/10.1016/j.ijcard.2019.05.046.
17. Li X, Fan X, Li S, et al. A novel risk stratification score for sudden cardiac death prediction in middle-aged, nonischemic dilated cardiomyopathy patients: The ESTIMATED Score. *Can J Cardiol.* 2020;36: 1121-9. https://doi.org/10.1016/j.cjca.2019.11.009.
18. Ilov NN, Boytsov SA, Stompel DR, et al. Echocardiographic Predictors of Ventricular Tachyarrhythmias in Patients With Cardioverter-Defibrillator Implanted for Primary Prevention of Sudden Cardiac Death. Results From a two-Year Prospective Follow-up Study. *Kardiologiia*. 2022;62(11): 11-18 (In Russ.). https://doi.org/10.18087/cardio.2022.11.n2122.
19. Ilov NN, Surikova ON, Boytsov SA, et al. Possibilities

for predicting ventricular tachyarrhythmias in patients with heart failure with reduced ejection fraction based on surface electrocardiography. First results from a single-center prospective study. *Russian Journal of Cardiology.* 2021;26(12): 4661. (IN Russ.). doi:10.15829/1560-4071-2021-4661

20. Ilov NN, Boitsov SA, Krivosheev YuS, et al. Cardiac resynchronization therapy: potential for arrhythmic risk modification. *Cardiovascular Therapy and Prevention.* 2023;22(5): 3555. (In Russ.). https://doi.org/10.15829/1728-8800-2023-3555.

21. Ilov NN, Petrova OV, Tverdokhlebova DK, et al. Importance of blood biomarker determination in the selection of patients with heart failure for cardioverter-defibrillator implantation. C*ardiovascular Therapy and Prevention.* 2023;22(9): 3681. (In Russ.). https://doi.org/10.15829/1728-8800-2023-3681.

22. Ilov NN, Palnikova OV, Stompel DR, et al. Clinical Predictors of Occurrence of Ventricular Tachyarrhythmias in Patients with Reduced Left Ventricle Ejection Fraction. Results of Single-Center Prospective Study. *Kardiologiia*. 2021;61(5): 32-40 (In Russ.). https://doi.org/10.18087/CARDIO.2021.5.N1480.

23. Tereshchenko SN, Galyavich AS, Uskach TM, et al. 2020 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology.* 2020;25(11): 4083. (In Russ.). doi:10.15829/1560-4071-2020-4083.

24. Kleemann T, Strauss M, Kouraki K, et al. Contemporary benefit-harm profile over two decades in primary prophylactic ICD-therapy. *Clin Cardiol.* 2019;42: 866-72. https://doi.org/10.1002/clc.23234.

25. Halliday BP, Cleland JGF, Goldberger JJ, et al.. Personalizing Risk Stratification for Sudden Death in Dilated Cardiomyopathy: The Past, Present, and Future. *Circulation.* 2017;136: 215-31. https://doi.org/10.1161/CIRCULATIONAHA.116.027134.

26. Ilov NN, Palnikova OV, Stompel DR, et al. Risk stratification of sudden cardiac death in heart failure patients: is left ventricular ejection fraction alone sufficient? *Russian Journal of Cardiology.* 2021;26(1): 3959. (In Russ.). https://doi.org/10.15829/1560-4071-2021-3959.

27. Bilchick KC, Wang Y, Cheng A, et al. Seattle Heart Failure and Proportional Risk Models Predict Benefit From Implantable Cardioverter-Defibrillators. *J Am Coll Cardiol.* 2017;69: 2606-18. https://doi.org/10.1016/j.jacc.2017.03.568.

28. Levy WC, Lee KL, Hellkamp AS, et al. Maximizing Survival Benefit With Primary Prevention Implantable Cardioverter-Defibrillator Therapy in a Heart Failure Population. *Circulation*. 2009;120: 835-42. https://doi.org/10.1161/CIRCULATIONAHA.108.816884.

29. Vazquez R, Bayes-Genis A, Cygankiewicz I, et al. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J.* 2009;30: 1088-96. https://doi.org/10.1093/eurheartj/ehp032.

30. Shen L, Claggett BL, Jhund PS, et al. Development and external validation of prognostic models to predict sudden and pump-failure death in patients with HFrEF from PARADIGM-HF and ATMOSPHERE. *Clin Res Cardiol.* 2021;110: 1334-49. https://doi.org/10.1007/s00392-021-01888-x.

31. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events. *N Engl J Med.* 2009;361: 1329-38. https://doi.org/10.1056/NEJMoa0906431.

32. Moss AJ, Schuger C, Beck CA, et al. Reduction in Inappropriate Therapy and Mortality through ICD Programming. *N Engl J Med.* 2012;367: 2275-83. https://doi.org/10.1056/NEJMoa1211107.

33. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *Eur Heart J.* 2021;42: 1676-84. https://doi.org/10.1093/eurheartj/ehaa1057.

34. Zareba W, Daubert JP, Beck CA, et al. Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators. *J Am Coll Cardiol.* 2018;72: 636-45. https://doi.org/10.1016/j.jacc.2018.04.086.

35. Ilov NN, Boytsov SA, Nechepurenko AA. Whether to implant a defibrillator or not? The Possibility of Using the MADIT-ICD Benefit Score Calculator in Real Practice. *Kardiologiia.* 2024;64: 27-33. https://doi.org/10.18087/cardio.2024.2.n2447.

https://doi.org/10.35336/VA-1387

SYSTOLIC, DIASTOLIC, AND PULSE BLOOD PRESSURE DURING PREMATURE VENTRICULAR CONTRACTIONS: RELATIONSHIP WITH CHARACTERISTICS OF ECTOPIC BEATS

Yu.V.Shubik[1], A.B.Korneev[1], M.A.Baturova[2], A.N.Morozov[3], V.V.Pivovarov[4], G.K.Zaytsev[4], V.M. Tikhonenko[1], A.Yu.Kormilytsin[4], M.V.Gordeeva[1], M.V.Berman[1]

[1]St. Petersburg State University, Russia, St. Petersburg, 7-9 Universitetskaya emb.; [2]OOO Northwest Center for Diagnosis and Treatment of Arrhythmias, Russia, St. Petersburg, 40-4 Lunacharsky ave.; [3]Pavlov First St. Petersburg State Medical University, Russia, St. Petersburg, 6-8 Lev Tolstoy str.; [4]NAO Incart, Russia, St. Petersburg. Russia, 12 Fermskoe road.

The aim is to assess the relationship between systolic, diastolic, and pulse blood pressure (SBP, DBP, PBP) during ventricular extrasystoles (VE) and the individual characteristics of ectopic beats.

Methods. The primary method of investigation was BP measurement for each heartbeat. Inclusion criteria were the presence of ≥10000 monomorphic VE per day. A total of 53 patients were included, either without structural heart changes or with minimal structural alterations. The mean of systolic, diastolic, and pulse BP (SBP, DBP, and PBP) during VE (SBP VE, DBP VE, PBP VE) and during post-extrasystolic sinus contraction (post VE SBP, post VE DBP, post VE PBP) were calculated for each patient as fractions of 1.0.

Results. The QRS complex width in VE originating from the right ventricular outflow tract is greater than from the left ventricular outflow tract; fragmentation of the QRS complex is more commonly observed in these VE. Significant correlations were observed between SBP VE and mean coupling interval (CI), PBP VE and CI, and SBP VE and PBP VE, though not between DBP VE and CI. DBP VE was significantly associated with VE count and daily VE percentage, while PBP VE was associated with left ventricular ejection fraction. It has been shown that post-VE SBP and post VE DBP are lower, while post VE PBP is higher compared to the corresponding parameters of sinus beats preceding the VE. Significant relationships were found between post VE SBP and post VE PBP, the duration of the post-extrasystolic pause, and the presence of paired VE; between post VE DBP and post VE PBP, DBP VE, CI VE, the presence of non-sustained ventricular tachycardia, and daily VE percentage; between post VE PBP and DBP VE, the presence of non-sustained ventricular tachycardia, daily VE percentage, and post-extrasystolic pause duration. Post VE PBP was equally determined by values of post VE SBP and DBP.

Conclusion. With the shortening of the VE coupling interval, its SBP decreases, while DBP increases slightly, which may determine its hemodynamic significance. In post-extrasystolic sinus beats, both SBP and DBP decrease.

Key words: ventricular extrasystole; premature ventricular contractions; arrhythmia-associated cardiomyopathy; “beat-to-beat” method; measurement of systolic, diastolic, pulse arterial pressure at each heartbeat; postextrasystolic potentiation; hemodynamic effectiveness; Holter electrocardiogram monitoring

Conflict of Interest: none.
Funding: none.
Received: 30.06.2024 **Revision received:** 02.12.2024 **Accepted:** 03.12.2024
Corresponding author: Yuri Shubik, E-mail: yshubik@mail.ru

Yu.V.Shubik - ORCID ID 0000-0002-8736-1575, A.B.Korneev - ORCID ID 0000-0002-6796-8302, M.A.Baturova - ORCID ID 0000-0003-3811-6810, A.N.Morozov - ORCID ID 0000-0003-2598-7000, V.V.Pivovarov - ORCID ID 0000-0002-8426-215X, G.K.Zaytsev - ORCID ID 0000-0002-8822-9197, V.M.Tikhonenko - ORCID ID 0000-0002-6262-1326, A.Yu.Kormilytsin - ORCID ID 0000-0002-6373-4285, M.V.Gordeeva - ORCID ID 0000-0002-9437-8535, M.V.Berman - ORCID ID 0000-0001-9554-5553.

For citation: Shubik YuV, Korneev AB, Baturova MA, Morozov AN, Pivovarov VV, Zaytsev GK, Tikhonenko VM, Kormilytsin AYu, Gordeeva MV, Berman MV. Systolic, diastolic, and pulse blood pressure during premature ventricular contractions: relationship with characteristics of ectopic beats. *Journal of Arrhythmology.* 2024;31(4): 59-68. https://doi.org/10.35336/VA-1387.

When evaluating the clinical significance of any cardiac rhythm disturbances, three primary aspects are typically considered: symptomatology and its impact on the patient’s quality of life; increased risk of sudden cardiac death (SCD); and the development and progression of chronic heart failure (CHF). These aspects are relevant for both supraventricular and ventricular arrhythmias.

For example, the potential for psychogenic reactions in patients with supraventricular tachycardias (SVTs), various forms of atrial fibrillation (AF) and flutter, and ventricular extrasystole (VE) and tachycardia is well-established [1, 2]. All these arrhythmias are associated with increased mortality, including SCD [9-15]. VEs, in particular, are recognized for their potential to trigger life-threatening

ventricular arrhythmias, such as monomorphic and polymorphic ventricular tachycardias, ventricular flutter, and fibrillation, which may result in SCD [14-16]. The risk is especially high in patients with underlying structural or genetic heart diseases, including channelopathies and cardiomyopathies [17-29].

Another significant clinical consequence of rhythm disturbances is their potential to cause arrhythmia-associated cardiomyopathies (AACs). Contemporary guidelines on managing AF, SVTs, ventricular arrhythmias, and SCD prevention have dedicated sections discussing AACs [17-19, 30, 31]. AACs are linked to tachyarrhythmias due to a high heart rate and, in the case of VEs, to the frequency of ventricular ectopy. The greater the VE burden detected via 24-hour Holter electrocardiography (ECG), the higher the likelihood of AAC development.

The 2020 Russian Ministry of Health guidelines recommend addressing VEs either pharmacologically or via catheter ablation if they are associated with clinical symptoms or lead to ventricular dilation and reduced left ventricular (LV) myocardial contractility, provided they exceed 15% of total daily heartbeats [18]. The presence or absence of structural heart disease does not affect this recommendation. Meanwhile, the 2022 ESC guidelines set the "critical" VE burden at 10% [17]. For asymptomatic patients with "idiopathic" VEs exceeding 20% of daily beats, catheter ablation may be considered to prevent AAC. Similar criteria are being debated for inclusion in the forthcoming 2025 Russian Ministry of Health recommendations. Thus, VE burden is often viewed as the primary determinant of AAC risk.

However, VE burden alone may not fully capture the hemodynamic significance of VEs. Even a burden exceeding 20% does not always result in AAC over decades [32]. Factors such as QRS width and fragmentation (markers of ventricular dyssynchrony), morphology, coupling interval, polymorphism, and others may play a role [19, 33-35], potentially influenced by the arrhythmogenic substrate's location.

The hemodynamic insufficiency of premature beats can be assessed using parameters such as reduced systolic blood pressure (SBP), elevated diastolic blood pressure (DBP), and changes in pulse blood pressure (PBP) as an integral metric. The clinical significance of postextrasystolic potentiation (PESP)-the hemodynamic characteristics of sinus beats following compensatory pauses after VEs-is also discussed in the literature [36-39]. Studies suggest a prognostically adverse role for PESP in CHF patients, those with prior myocardial infarction, and individuals with AAC caused by frequent VEs. Investigating SBP, DBP, and PBP of postextrasystolic contractions may provide insights into this phenomenon. These metrics are likely individualized, and their accurate assessment has been methodologically challenging.

Currently, blood pressure for individual heartbeats can be measured invasively (using an arterial catheter connected to a transducer) or noninvasively through methods such as photoplethysmography, continuous tonometric monitoring (Volume Clamp Method), impedance cardiography, or applanation tonometry. Beat-to-beat BP measurement is particularly relevant for evaluating patients with syncope [40, 41]. In this study, a method based on the "unloaded artery" principle, capable of capturing the complete BP waveform, was utilized. The degree of BP alteration during VEs largely determines their hemodynamic significance.

This study aimed to assess the relationship between systolic, diastolic, and pulse blood pressure during ventricular extrasystoles and the individual characteristics of ectopic beats

METHODS

The clinical study adhered to the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee at the "Northwest Center for Diagnosis and Treatment of Arrhythmias" (St. Petersburg, Russia). Written informed consent was obtained from all participants.

The primary inclusion criterion was the presence of at least 10,000 monomorphic VEs per day, as determined by Holter ECG monitoring. Exclusion criteria included the presence of any cardiomyopathy (including arrhythmia-induced cardiomyopathy) or channelopathy, clinically significant chronic heart failure, reduced left ventricular ejection fraction (LVEF), and acute or exacerbated chronic conditions. Patients with polymorphic VEs were also excluded if VEs of other morphologies accounted for more than 1% of their total daily count.

A total of 53 patients (21 men), aged between 16 and 87 years (mean age 56.5 ± 2.4 years), were included in the study. In 21 cases, idiopathic VE was the sole manifestation of the condition, constituting Group 1. Hypertension was diagnosed in 20 patients, and an additional 9 patients presented with a combination of hypertension and ischemic heart disease (Group 2). Myocarditic cardiosclerosis, as confirmed by gadolinium-enhanced magnetic resonance imaging (MRI), was diagnosed in 3 patients (Group 3). Structural, functional, and electrocardiographic characteristics of the patients are summarised in Table 1.

Additionally, paired VEs were detected in 32 cases, nonsustained ventricular tachycardia (VT) in 14 cases, and QRS complex fragmentation in VEs in 19 cases. Based on the results of 12-lead electrocardiograms (ECG) [44-47], the approximate localization of the arrhythmogenic substrate was assessed as follows: in 23 patients, the right

Table 1.

Some structural-functional and electrocardiographic characteristics

Indicator	M±m
LV EF, %	61.7±1.35
LV thickness, mm	9.93±0.33
QRS complex width during VE, ms	140.38±2.19
Average CI during VE, ms	539.3±13.59
Post-extrasystolic pause, ms	1053.86±28.92
Average number of VEs per day	18611.0±1743.8
Average % VEs*	17.8±1.7

Note: hereinafter, LVEF - left ventricle ejection fraction; CI - coupling interval; VE - ventricular extrasystole; * - of the total number of heartbeats per day.

ventricular outflow tract (RVOT); in 12 patients, the left ventricular outflow tract (LVOT); and in 18 patients, other locations.

In addition to the aforementioned data, the following key parameters were assessed in patients:

- Mean SBP, DBP, and PBP of the sinus beat preceding the VE;
- Mean SBP, DBP, and PBP during the VE;
- Mean SBP, DBP, and PBP of the sinus beat following the VE (designated as post-VE SBP, post-VE DBP, and post-VE PBP, respectively).

The average SBP, DBP, and PBP during VE (SBP VE, DBP VE, and PBP VE) and the average post-VE SBP, post-VE DBP, and post-VE PBP for each patient were determined as fractions of 1.0. The value of 1.0 corresponded to the average SBP, DBP, and PBP of the sinus beats preceding the VE.

The primary method of investigation was beat-to-beat blood pressure measurement using the "Cardiotechnika-SAKR" device (NAO Incart, St. Petersburg, Russia, patents RU 2694737 C1 by V.V. Pivovarov et al. and RU 2698447 C1 by V.V. Pivovarov et al.). This method has been previously described in our publications on beat-to-beat blood pressure measurement during persistent atrial fibrillation and VE [42, 43].

The method involves continuous analysis of the finger vessel volume using a photoplethysmographic signal and a tracking electropneumatic system, which generates pressure to counteract changes in the arterial diameter of the finger under a cuff. The distal blood pressure measurement is calibrated against brachial blood pressure by adjusting the continuous pressure signal to align with the moments of Korotkoff sounds, simultaneously recorded during conventional blood pressure measurement on the contralateral arm.

This technique enables measurement of SBP and DBP and the calculation of PBP for each individual heartbeat, whether sinus or ectopic. The duration of each measurement session, determining SBP, DBP, and PBP for every beat, was 15 minutes.

TTable 2.

Indicators characterizing the hemodynamic significance of ventricular extrasystole

Indicator	Value
SBP VE across the entire group of patients	0.73±0.09. p<0.0001
DBP VE across the entire group of patients	1.11±0.10. p<0.0001
PP VE across the entire group of patients	0.12±0.19. p<0.0001
Correlation between SBP VE and CI	r=0.65. p<0.0001
Correlation between DBP VE and CI	r=0.04. p=0.76
Correlation between PP VE and CI	r=0.81. p<0.0001
Correlation between SBP VE and PP VE	r=0.75. p<0.0001
Correlation between DBP VE and % VE	r=0.51. p<0.008
Correlation between DBP VE and nVE	r=0.45. p<0.02
Correlation between PP VE and LVEF	r=-0.43. p<0.02

Note: hereinafter, DBP - Diastolic Blood Pressure; VE - Premature Ventricular Contraction; PP - Pulse Pressure; SBP - Systolic Blood Pressure; nVE - Number of VEs per day

Statistical analysis

Statistical analysis was performed using the SPSS software package. Student's t-test was applied to compare the means of two groups. One-way analysis of variance (ANOVA) with Tukey's post hoc test was used for comparisons involving more than two groups. The Chi-square test (χ^2 test) was employed for the analysis of categorical data. Pearson›s correlation coefficient was used to assess the linear relationship between two quantitative variables. Multiple linear regression was applied to evaluate the influence of several independent variables on a dependent variable. A p-value of <0.05 was considered the threshold for statistical significance.

RESULTS

The first stage of data analysis involved characterising patient groups and identifying the features of VE. As expected, a statistically significant correlation was observed between patient age and the presence or absence of heart disease. The mean age of patients with heart disease was 65.00±2.10 years, while for those without heart disease it was 42.85±3.82 years (p<0.0001).

Age was also correlated with the localisation of the arrhythmogenic substrate. The mean age of patients with VE originating from the right ventricular outflow tract (RVOT) was 46.61±3.19 years, compared to 59.42±4.73 years for VE from the left ventricular outflow tract (LVOT), and 67.61±3.45 years for other localisations. Differences between RVOT and LVOT were not statistically significant (p=0.059), whereas differences between RVOT and other localisations were highly significant (p=0.0002). Among the 23 patients with RVOT-originating VE, the arrhythmia was idiopathic in 17 cases. In contrast, only 2 of 12 patients with LVOT-originating VE and 1 of 18 with other localisations had idiopathic VE. The differences were statistically significant between RVOT and LVOT (p=0.003), and even more so between RVOT and other localisations (p=0.00002).

The left ventricular (LV) wall thickness in patients with idiopathic VE was 8.5±1.17 mm, compared to 11.42±1.02 mm in patients with hypertension (HTN) or a combination of HTN and coronary artery disease (CAD), and 10.83±1.22 mm in patients with post-myocarditis cardiosclerosis. Statistically significant differences were found between the first and second groups (p<0.05) and between the first and third groups (p<0.05), but not between the second and third groups (p>0.05). Similar differences were observed in LV wall thickness based on the localisation of the arrhythmogenic substrate: RVOT 8.50±0.34 mm, LVOT 11.42±0.42 mm, and other localisations 10.83±0.41 mm. Significant differences were found between RVOT and LVOT (p=0.0001) and between RVOT and other localisations (p=0.0004).

The LVEF did not differ significantly between groups with and without organic heart disease. No significant differences were found in the number of VE per day on Holter ECG monitoring or the percentage of VEs over 24 hours among

patients with different arrhythmogenic substrate localisations. The mean QRS duration of VEs was significantly longer for VEs originating from the right ventricular outflow tract (RVOT) (147.8±3.3 ms) compared to those from the left ventricular outflow tract (LVOT) (131.7±3.7 ms; p=0.049). These findings align with data on QRS fragmentation: fragmentation was not observed in any of the 12 patients with LVOT-originating VEs, but was present in 13 of 23 patients with RVOT-originating VEs and in 6 of 18 patients with other localisations. The differences in QRS fragmentation between RVOT and LVOT were also statistically significant (p=0.0008).

The mean coupling interval (CI) of VEs originating from the RVOT was 518.7±11.9 ms, compared to 525.0±29.4 ms for LVOT-originating VEs and 575.2±30.7 ms for other localisations. No statistically significant differences were observed between these groups. When combining RVOT and LVOT localisations and comparing them to all other localisations, the mean CI values (520.7±12.5 ms vs. 575.2±30.7 ms) also did not differ significantly. Excluding patients with interpolated VEs, allorhythmias, or obvious parasystole from the analysis did not significantly affect these findings.

The second stage of analysis focused on assessing SBP VE, DBP VE, and PBP VE as parameters largely defining the hemodynamic significance of VEs. These values were calculated as fractions of 1.0, where 1.0 represented the SBP, DBP, and PBP of sinus beats preceding the VEs. The results are presented in Table 2. SBP VE, DBP VE, and PBP VE did not significantly differ across patient groups with varying arrhythmogenic substrate localisations, nor were they influenced by QRS duration or fragmentation. Similarly, no differences in these parameters were observed between patients with idiopathic VEs and those with hypertension (HTN), combined HTN and coronary artery disease (CAD), or myocarditis-related cardiosclerosis.

However, SBP VE was closely associated with mean CI: as mean CI decreased, SBP VE also decreased. This relationship is illustrated graphically in Figure 1.

The correlation between the mean coupling interval (mean CI) and diastolic blood pressure during VEs (DBP VE) was not statistically significant. Pulse blood pressure during VEs (PBP VE) was more strongly associated with mean CI than systolic blood pressure during VEs (SBP VE): as mean CI decreased, PBP VE also decreased. Thus, PBP VE was determined by SBP VE but not by DBP VE. A close correlation was observed between SBP VE and PBP VE. Figure 2 graphically illustrates the relationships between SBP VE, DBP VE, and PBP VE. It is evident that the reduction in PBP VE was minimally influenced by an increase in DBP VE and was primarily determined by a decrease in SBP VE.

Apart from these relationships, DBP VE showed a statistically significant correlation (in decreasing order of strength) with the percentage of VEs over 24 hours and the total number of VEs per day on Holter ECG monitoring. The relationships of DBP VE with DBP post-VE (DBPpost VE), PBP post-VE (PBPpost VE), and the duration of the postextrasystolic pause are discussed in a subsequent section.

For PBP VE, a statistically significant correlation was found with LVEF. No correlations were found with other parameters. Excluding patients with interpolated VEs or apparent parasystole did not significantly alter these findings. However, the correlation between SBP VE and LVEF became statistically significant (r = -0.47, p=0.02).

The third stage of analysis focused on characterising the phenomenon of PESP. No significant differences were observed in the duration of the postextrasystolic pause between groups with and without organic heart disease or across different arrhythmogenic substrate localisations. The pause duration correlated with mean CI (r = 0.39, p=0.004) and DBP VE (r = 0.24, p=0.03).

Postextrasystolic SBP (SBPpost VE), DBPpost VE, and PBPpost VE were evaluated as indicators reflecting PESP characteristics. These values were calculated as fractions of 1.0, where 1.0 represented SBP, DBP, and PBP of sinus beats preceding the VEs. Unlike most published studies, which compared postextrasystolic SBP with SBP from 8–10 subsequent sinus beats, this study evaluated PESP based on single postextrasystolic beats due to the high VE burden (≥10,000 VEs/day, up to 45,000/day) per the inclusion criteria.

The results are presented in Table 3. Differences in SBPpost VE, DBPpost VE, and PBPpost VE compared to their respective pre-VE sinus values were relatively minor but highly statistically significant, with small standard deviations. These values were independent of the arrhythmogenic substrate localisation, QRS width, or QRS fragmentation. Similarly, no differences were found between patients with idiopathic VEs, those with hypertension (including combined hypertension and CAD), or myocarditis-related cardiosclerosis.

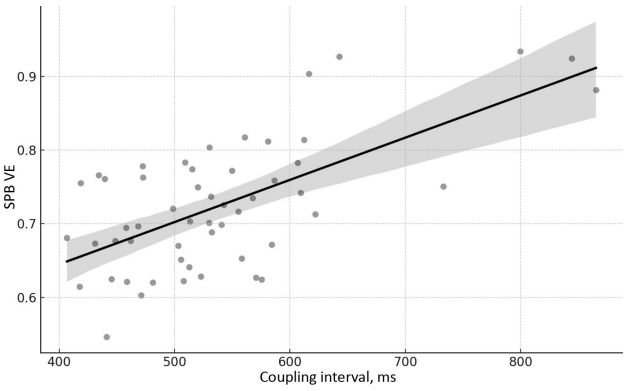

Figure 1. Relationship between CI and SBP during VE.

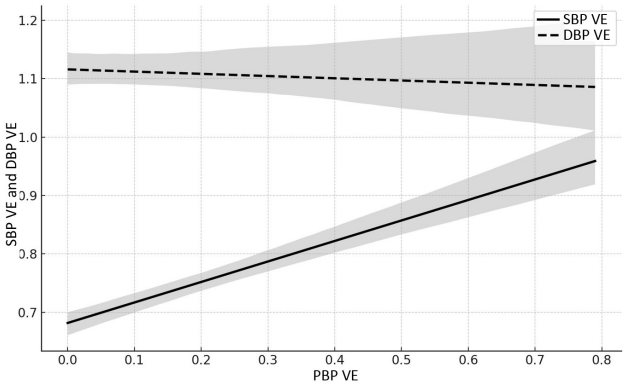

Figure 2. Relationship among SBP, DBP, and PBP during VE.

Excluding interpolated VEs and apparent parasystole from the analysis did not affect the results, except for the correlation between PBPpost VE and the number of VEs per day, which, along with the percentage of VEs, became statistically significant (r = -0.56, p=0.007).

A statistically significant correlation was observed between SBPpost VE and the duration of the compensatory pause (Figure 3), as well as between PBPpost VE and the duration of the compensatory pause. In contrast, the correlation between DBPpost VE and the postextrasystolic pause duration was not statistically significant.

The formation of the integral PBPpost VE parameter differed substantially from PBP VE. While the latter was primarily determined by SBP VE with minimal dependence on DBP VE, PBPpost VE was equally influenced by SBPpost VE and DBPpost VE, as shown in Figure 4.

DISCISSION

The determination of treatment strategies for VEs, as outlined in modern guidelines, is primarily based on the presence or absence of structural heart changes. Another crucial factor is symptomatology and the frequency of VEs. The number of ectopic beats directly correlates with the likelihood of developing AAC, regardless of the presence or absence of organic heart disease. However, in clinical practice, the progression to AAC varies among patients: some with a high VE burden develop AAC relatively quickly, while others remain unaffected over many years or even decades of observation[32].

In limited publications, several additional hemodynamically significant characteristics of VEs have been proposed as contributors to AAC formation. These include QRS width and fragmentation, morphology, prematurity index, and polymorphism. The *beat-to-beat* blood pressure measurement method allows the evaluation of these and other properties of VEs, enabling an understanding of their potential hemodynamic significance.

A key feature of VEs, as premature cardiac contractions, is their significant reduction in SBP. This reduction is attributed to insufficient ventricular filling, leading to decreased stroke volume and impaired cardiac pump function. Increased DBP may also play a role as a potential contributor to LV diastolic dysfunction. Additionally, the shortening of diastolic duration-the phase during which myocardial perfusion via coronary arteries occurs-can further compromise the blood supply to the myocardium. PBP, as a composite measure of SBP and DBP, emphasizes these changes when present.

The method also facilitates the evaluation of an intriguing, yet underexplored, property of VEs termed PESP. The existing literature on PESP presents conflicting findings. Physiological increases in SBP during sinus contractions following a compensatory pause have been attributed to enhanced contractility caused by elevated intracellular calcium levels in cardiomyocytes during the pause. Conversely, pathological conditions, such as chronic heart failure and myocardial infarction, have been associated with reduced SBP due to inadequate ventricular filling, which diminishes stroke volume. DBP typically remains unchanged but may increase in cases of LV diastolic dysfunction.

This study included patients with a high number of monomorphic VEs. Arrhythmogenic substrate localization was determined approximately using a standard 12-lead ECG. Following current guidelines, two groups were identified: those with RVOT arrhythmogenic substrate" and "all other localizations," which differ in treatment approaches. Additionally, a third group with "LVOT arrhythmogenic substrate" was analyzed based on ECG characteristics.

Table 3.

Indicators characterizing the hemodynamic significance of ventricular extrasystole

Indicator	Value
Post VE SBP across the entire patient group	0.98±0.05. p=0.02
Post VE DBP across the entire patient group	0.91±0.01. p<0.0001
Post VE PBP across the entire patient group	1.12±0.03. p=0.0001
Correlation between post VE SBP and post VE PBP	r=0.58. p=0.002
Correlation between post VE SBP and PEP	r=0.40. p=0.003
Correlation between post VE SBP and the presence of paired VEs	r=-0.40. p=0.04
Correlation between post VE DBP and post VE PBP	r=-0.61. p=0.001
Correlation between post VE DBP and VE DBP	r=0.51. p=0.008
Correlation between post VE DBP and CI of VE	r=0.48. p=0.01
Correlation between post VE DBP and the presence of NSVT	r=0.44. p=0.03
Correlation between post VE DBP and daily VE percentage	r=0.43. p=0.03
Correlation between post VE PBP and VE DBP	r=-0.52. p=0.01
Correlation between post VE PBP and the presence of NSVT	r=-0.48. p=0.03
Correlation between post VE PBP and daily VE percentage	r=-0.41. p=0.04
Correlation between post VE PBP and PEP	r=0.38. p=0.005

Note: hereinafter, PEP - Post-extrasystolic pause NSVT - Non-sustained ventricular tachycardia.

Inclusion criteria mandated either the absence of structural heart changes or minimal structural abnormalities. Patients with significant LV hypertrophy, previous myocardial infarction, clinically significant chronic heart failure, reduced pump function, or chamber enlargement-including those with a history of myocarditis-were excluded. Among hypertensive patients, the mean LV wall thickness was 11.4 mm, while in other groups, it remained within normal limits. LVEF was within normal ranges and did not differ significantly among the patient groups.

The present study included patients with a high number of monomorphic VEs. Arrhythmogenic substrate localization was determined approximately using a standard 12-lead ECG. Following current guidelines, patients were divided into two groups: "RVOT arrhythmogenic substrate localiza-

tion" and "all other localizations," which differed in treatment approaches. Additionally, a third group of patients with "LVOT arrhythmogenic substrate localization," easily identifiable by ECG, was included.

Inclusion criteria required the absence of structural heart changes or minimal structural abnormalities. Patients with significant left ventricular hypertrophy, prior myocardial infarction, clinically significant chronic heart failure, reduced pump function, or chamber enlargement-including those with a history of myocarditis-were excluded. Even among patients with hypertension, the mean LV wall thickness was only 11.4 mm, and for others, it did not exceed normal limits. LVEF was within normal ranges and did not differ significantly among the patient groups.

As expected, patients with "idiopathic" VEs were significantly younger. These patients were more likely to have arrhythmogenic substrates localized in the RVOT. Patients with LVOT VEs were older, while those with VEs from other sources were the oldest.

An interesting finding was the differences in the characteristics of the QRS complex during VEs based on arrhythmogenic substrate localization. VEs originating from the RVOT were wider than those from the LVOT. Half of the RVOT VEs showed fragmentation (similar to VEs from other localizations), whereas none of the LVOT VEs exhibited this phenomenon. These differences may reflect the nature of excitation propagation during VEs, even though the RVOT and LVOT are anatomically close.

The mean CI of VEs did not differ significantly between different arrhythmogenic substrate localizations. Factors such as a large number of interpolated VEs or evident parasystole with classical signs could have influenced the analysis. However, excluding such patients from the sample did not substantially alter the results.

In the second stage of the analysis, SBP, DBP, and PBP during VEs were evaluated as indicators that largely characterize the hemodynamic significance of ectopic contractions. Significant reductions in SBP and non-significant increases in DBP during VEs were observed. The most important characteristic of VEs, likely determining their hemodynamic significance, was the CI. No correlation was found with other parameters, such as arrhythmogenic substrate localization, QRS width, QRS fragmentation, or the presence of organic heart disease. The reduction in the integral PBP during VEs was minimally related to the increase in DBP and was primarily determined by the decrease in SBP.

A correlation between diastolic blood pressure during premature ventricular contractionsq and the number of VEs was established, indicating that DBP VE increases as the VE count rises. This correlation is logical, as a higher number of VEs reduces the overall relaxation and filling time of the heart. However, the observed inverse relationship between LVEF and both systolic blood pressure during VEs (SBP VE) and pulse blood pressure during VEs (PBP VE) is less straightforward. It appears that higher LVEF reduces the need for compensatory mechanisms, such as sympathetic nervous system activation, which might otherwise increase SBP.

The third stage of analysis explored the phenomenon of PESP. An interesting finding was the correlation between the mean CI and the duration of the compensatory pause; longer CIs were associated with longer pauses. This may be due to ventriculo-atrial conduction of VEs and the discharge or non-discharge of the sinus node.

Analysis of post-VE SBP, DBP, and PBP revealed that the presence of PESP should be interpreted cautiously. Post-VE SBP was slightly lower than the SBP of sinus beats preceding VEs. Post-VE DBP decreased modestly but not markedly. Post-VE PBP increased significantly; however, unlike VE beats, its changes were equally influenced by both post-VE SBP and DBP (with DBP having a slightly greater impact). As with VE-related SBP, DBP, and PBP, PESP characteristics showed no dependence on the localization of the arrhythmogenic substrate, QRS width or fragmentation, or the presence of structural heart disease. Post-VE SBP increased with longer compensatory pauses, which is consistent with physiological expectations. A weak but significant correlation was observed between reduced post-VE SBP and paired VEs, likely because two consecutive VEs share a single compensatory pause.

The correlation between post-VE DBP and DBP VE is straightforward and expected, whereas its positive association with CI suggests reflexive sympathetic activation due to baroreceptor stimulation. This could increase vascular tone, elevating post-VE DBP. However, while a significant relationship between CI and the compensatory pause duration was observed, post-VE DBP did not show a statistically significant link to the pause duration.

The relationship between post-VE DBP and the number of VEs (including VE percentages during Holter monitoring and the presence of non-sustained ventricular tachycardia) is logical and reflects insufficient ventricular relaxation during diastole. Consequently, the integral indi-

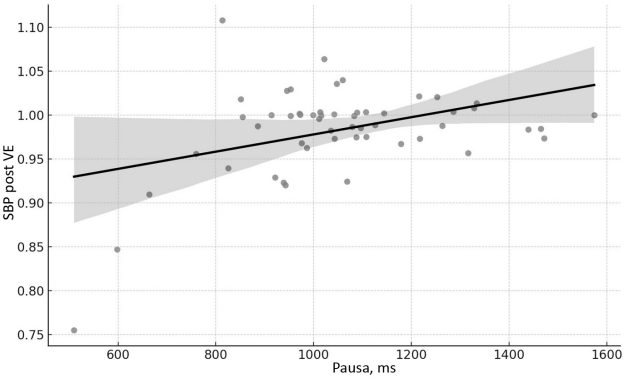

Figure 3. Relationship between post VE SBP and the duration of the compensatory pause.

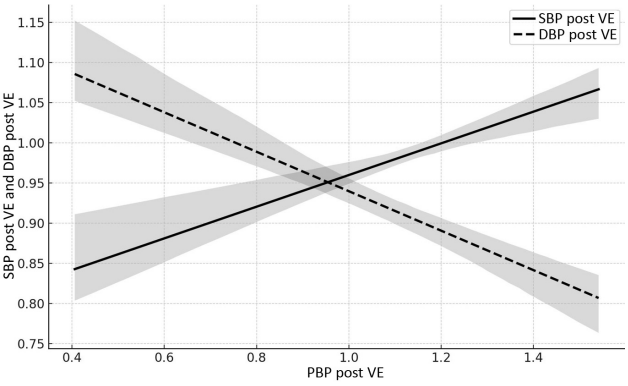

Figure 4. Relationship among post VE SBP, post VE DBP, and post VE PBP.

cator post-VE PBP correlates with the VE count and compensatory pause duration.

The study's foundation was the non-invasive determination of SBP, DBP, and PBP for each heartbeat. This enabled the assessment of hemodynamic properties of both ectopic and post-compensatory beats, providing insights into the PESP phenomenon. A notable feature influencing the study's outcomes was the selection of patients with no or minimal structural heart changes. Therefore, the findings should not be extrapolated to patients with clinically significant heart failure, previous myocardial infarction, severe LV hypertrophy, or other serious organic heart conditions. This important limitation is also a strength of the study, as it provides reference hemodynamic characteristics for VEs (SBP, DBP, PBP, post-VE SBP, DBP, and PBP) applicable to patients with frequent VEs. The most significant findings of this research can be summarized as follows.

CONCLUSION

1. Premature ventricular contractions, as hemodynamically ineffective cardiac beats, are characterised by a reduction in systolic blood pressure and, to a lesser extent, an increase in diastolic blood pressure.
2. SBP VE and pulse blood pressure during VEs decrease as the coupling interval shortens; no significant correlation was found between CI and DBP VE.
3. Post-VE SBP and DBP are lower, whereas post-VE PBP is higher than the corresponding values of sinus beats preceding VEs; the differences are small but statistically significant.
4. The examined characteristics (SBP VE, DBP VE, PBP VE, post-VE SBP, post-VE DBP, and post-VE PBP) were not dependent on QRS width or fragmentation or the localization of the arrhythmogenic substrate.

REFERENCES

1. Ying Du, Shanshan Ma, Pan Yue, et al. Comparing the effects of pulsed and radiofrequency catheter ablation on quality of life, anxiety, and depression of patients with paroxysmal supraventricular tachycardia: a single-center, randomized, single-blind, standard-controlled trial. *Trials.* 2024;25(1): 146. https://doi.org/10.1186/s13063-024-07971-8.
2. Medi C, Kalman JM, Freedman SB. Supraventricular tachycardia. *Med J Aust.* 2009;190(5): 255-60. https://doi.org/10.5694/j.1326-5377.2009.tb02388.x.
3. Lomper K, Ross C, Uchmanowicz I. Anxiety and Depressive Symptoms, Frailty and Quality of Life in Atrial Fibrillation. *Int J Environ Res Public Health.* 2023;20(2): 1066. https://doi.org/10.3390/ijerph20021066.
4. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest.* 2007;132(4): 1259-64. https://doi.org/10.1378/chest.07-0036.
5. Yakovenko TV, Shubik YuV, Kostyuk GP, Kryatova TV. Structure and dynamics of nosogenic psychic reactions in patients with different forms of atrial fibrillation. *Journal of arrhythmology.* 2006;44: 26-29 (In Russ.).
6. Yakovenko TV, Shubik YuV, Kostyuk GP, Kryatova TV. The quality of life of patients with various forms of atrial fibrillation and the effect on it of treatment of nosogenic psychic reactions. *Journal of arrhythmology.* 2008;51: 36-39 (In Russ.).
7. Mikhaylov AY, Yumashev AV, Kolpak E. Quality of life, anxiety and depressive disorders in patients with extrasystolic arrhythmia. *Arch Med Sci.* 2020;18(2): 328-335. https://doi.org/10.5114/aoms.2020.101359.
8. Sandhu U, Kovacs AH, Nazer B. Psychosocial symptoms of ventricular arrhythmias: Integrating patient-reported outcomes into clinical care. *Heart Rhythm O2.* 2021;2(6Part B): 832-839. https://doi.org/10.1016/j.hroo.2021.09.011.
9. Sandhu U, Nguyen AT, Dornblaser J, et al. Patient-Reported Outcomes in a Multidisciplinary Electrophysiology-Psychology Ventricular Arrhythmia Clinic. *J Am Heart Assoc.* 2022;11(15): e025301. https://doi.org/10.1161/JAHA.122.025301.
10. Marazzato J, Angeli F, De Ponti R, et al. Atrial fibrillation and sudden cardiac death: a mystery to unravel? *G Ital Cardiol (Rome).* 2021;22(7): 544-553. https://doi.org/10.1714/3629.36105.
11. Waldmann V, Jouven X, Narayanan K, et al. Association Between Atrial Fibrillation and Sudden Cardiac Death: Pathophysiological and Epidemiological Insights. *Circ Res.* 2020;127(2): 301-309. https://doi.org/10.1161/CIRCRESAHA.120.316756.
12. Obeyesekere MN, Leong-Sit P, Massel D, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. *Circulation.* 2015;125(19): 2308-15. https://doi.org/10.1161/CIRCULATIONAHA.111.055350.
13. Tang PT, Shenasa M, Boyle NG. Ventricular Arrhythmias and Sudden Cardiac Death. *Card Electrophysiol Clin.* 2017;9(4): 693-708. https://doi.org/10.1016/j.ccep.2017.08.004.
14. Krummen DE, Ho G, Villongco CT, et al. Ventricular fibrillation: triggers, mechanisms and therapies. *Future Cardiol.* 2016;12(3): 373-90. https://doi.org/10.2217/fca-2016-0001.
15. Boudoulas H, Dervenagas S, Schaal SF, et al. Malignant premature ventricular beats in ambulatory patients. *Ann Intern Med.* 1979 Nov;91(5): 723-6. https://doi.org/10.7326/0003-4819-91-5-723.
16. Von Olshausen K, Treese N, Pop T, et al. Sudden cardiac death in long-term electrocardiography. *Dtsch Med Wochenschr.* 1985 Aug 2;110(31-32): 1195-201.
17. Zeppenfeld K, Tfelt-Hansen J, De Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal.* 2022);00:1-130 https://doi.org/10.1093/eurheartj/ehac262.
18. Lebedev DS, Mikhailov EN, Neminuschiy NM, et al. Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. *Russian Journal of Cardiology.* 2021;26(7): 4600. (In Russ.) https://doi.org/10.15829/1560-4071-2021-4600.
19. Dan G-A, Martinez-Rubio A, Agewall S, et al. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology

(ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace*. 2018;20(5): 731-732an. https://doi.org/10.1093/europace/eux373.
20. Agesen FN, Lynge TH, Blanche P, et al. Temporal trends and sex differences in sudden cardiac death in the Copenhagen City Heart Study. *Heart.* 2021;107: 1303-1309. https://doi.org/10.1136/heartjnl-2020-318881.
21. Shkolnikova MA, Shubik YuV, Shalnova SA, et al. Cardiac Arrhythmias in Elderly Patients and Their Correlation with Health Indices and Mortality. *Journal of arrhythmology.* 2007;49: 5-13 (In Russ.).
22. Wilde AAM, Amin AS. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy. *JACC Clin Electrophysiol*. 2018;4(5): 569-579. https://doi.org/10.1016/j.jacep.2018.03.006.
23. Skinner JR, Winbo A, Abrams D, et al. Channelopathies That Lead to Sudden Cardiac Death: Clinical and Genetic Aspects. *Heart Lung Circ.* 2019;28(1): 22-30. https://doi.org/10.1016/j.hlc.2018.09.007.
24. Schimpf R, Veltmann C, Wolpert C, Borggrefe M. Arrhythmogenic hereditary syndromes: Brugada Syndrome, long QT syndrome, short QT syndrome and CPVT. *Minerva Cardioangiol.* 2010;58(6): 623-36.
25. Collis R, Elliott PM. Sudden cardiac death in inherited cardiomyopathy. *Int J Cardiol.* 2017;237: 56-59. https://doi.org/10.1016/j.ijcard.2017.04.006.
26. Gordeeva MV, Veleslavova OE, Baturova MA, et al. Sudden non-violent death in young adults (retrospective analysis). *Journal of arrhythmology*. 2011;65: 25-32 (In Russ.)
27. Gordeeva MV, Mitrofanova LB, Pahomov AV, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia as the cause of sudden cardiac death in young adults. *Journal of arrhythmology.* 2012;69: 38-48 (In Russ.)
28. Sedov VM, Yashin SM, Shubik YuV. Arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Journal of arrhythmology.* 2000;20: 23-30 (In Russ.)
29. Ryabkova VA, Churilov LP, Shoenfeld Y, et al. Lethal immunoglobulins: auto antibodies and sudden cardiac death. *Autoimmunity Reviews.* 2019;18(4): 415-425.
30. Arakelyan MG, Bockeria LA, Vasilieva EYu, et al. 2020 Clinical guidelines for Atrial fibrillation and atrial flutter. *Russian Journal of Cardiology.* 2021;26(7): 4594. (In Russ.). https://doi.org/10.15829/1560-4071-2021-4594
31. Bokeria LA, Golukhova EZ, Popov SV, et al. 2020 Clinical practice guidelines for Supraventricular tachycardia in adults. *Russian Journal of Cardiology.* 2021;26(5): 4484. (In Russ.).
32. Shubik YuV, Korneev AB, Morozov AN. Number of ventricular premature beats and other causes of cardiomyopathy associated with arrhythmia: case reports.. *Journal of arrhythmology.* 2023;30(4): e11-e15. https://doi.org/10.35336/VA-1237.
33. Latchamsetty R, Bogun F. Premature Ventricular Complex-Induced Cardiomyopathy. *JACC Clin Electrophysiol.* 2019;5(5): 537-550. https://doi.org/10.1016/j.jacep.2019.03.013.
34. Saurav A, Smer A, Abuzaid A, et al. Premature ventricular contraction-induced cardiomyopathy. *Clin Cardiol.* 2015;38(4): 251-8. https://doi.org/10.1002/clc.22371.
35. Treshkur TV, Tulintseva TE, Tatarinova AA, et al. Ventricular arrhythmias and holter monitoring - principles of formation of the conclusion on the results of the study. *Journal of arrhythmology.* 2018; 93: 53-63. (In Russ.). https://doi.org/10.25760/VA-2018-93-53-63.
36. Steger A, Sinnecker D, Barthel P, et al. Post-extrasystolic Blood Pressure Potentiation as a Risk Predictor in Cardiac Patients. *Arrhythmia & Electrophysiology Review.* 2016;5(1): 27-30. https://doi.org/10.15420/aer.2016.14.2.
37. Kuijer PJ, Van der Werf T, Meijler FL. Post-extrasystolic potentiation without a compensatory pause in normal and diseased hearts. *Br Heart J.* 1990;63(5): 284-6. https://doi.org/10.1136/hrt.63.5.284.
38. Mulpuru SK, Witt CM. Post-Extrasystolic Potentiation for Individualizing Care of Premature Ventricular Contraction-Induced Cardiomyopathy. *JACC Clin Electrophysiol.* 2017;3(11): 1292-1295. https://doi.org/10.1016/j.jacep.2017.07.010.
39. Sprenkeler DJ, Vos MA. Post-extrasystolic Potentiation: Link between Ca(2+) Homeostasis and Heart Failure? *Arrhythm Electrophysiol Rev.* 2016;5(1): 20-6. https://doi.org/10.15420/aer.2015.29.2.
40. Brignole M, Moya A, Frederik J. de Lange FJ, et al. Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. *European Heart Journal.* 2018;39: e43-e80. https://doi.org/10.1093/eurheartj/ehy071.
41. Thijs RD, Brignole M, FalupPecurariu C, et al. Recommendations for tilt table testing and other provocative cardiovascular autonomic tests in conditions that may cause transient loss of consciousness. *Clinical Autonomic Research.* 2021. https://doi.org/10.1007/s10286-020-00738-6.
42. Shubik YuV, Pivovarov VV, Zaytsev GK, et al. Blood pressure measuring at every heartbeat in atrial fibrillation patients: the next step towards the personalization of treatment strategy. *Journal of arrhythmology.* 2021;28(1): 23-32. (In Russ.) https://doi.org/10.35336/VA-2021-1-23-32.
43. [Shubik YuV, Korneev AB, Medvedev MM, Morozov AN. Hemodynamic features of different variants of the premature ventricular constractions. *Vestnik of Saint Petersburg University. Medicine.* 2023;18(3): 258-273 (In Russ.). https://doi.org/10.21638/spbu11.2023.303
44. Vainshtein AB, Yashin SM, Dumpis YaYu, Shubik YuV. Electrocardiographic topical diagnostics of non-coronary right ventricular arrhythmias. *Journal of arrhythmology.* 2004;34: 11-17. (In Russ.).
45. Revishvili Ash, Noskova MV, Rzaev FG, Artyuchina EV. Noninvasive topical diagnostics of non-coronary ventricular arrhythmias. *Journal of arrhythmology.* 2004;35: 5-15. (In Russ.).
46. Budanova MA, Chmelevsky MP, Treshkur TV, Tikhonenko VM. Electrocardiographic criteria and algorithms for differential diagnosis of wide QRS complexes arrhythmias. *Journal of arrhythmology.* 2020;27(4): 24-32. https://https://doi.org/10.35336/VA-2020-4-24-32. (In Russ.).
47. Taymasova IA, Yashkov MV, Dedukh EV, et al. History of development of ventricular arrhythmias diagnostics. *Kardiologiia.* 2021;61(12): 108-116. (In Russ.).

https://doi.org/10.35336/VA-1396

SYNCOPE, ASYSTOLE AND ATRIOVENTRICULAR BLOCK IN A CHILD WITH BREATH-HOLDING SPELLS: A CASE REPORT

L.M.Makarov[1,2], V.N.Komolyatova[1,2], I.I.Kiseleva[1], A.V.Dmitrieva[1]

[1]FSCC Children and Adolescents of the FMBA of Russia, Russia, Moscow, 20 Moskvorechye str.;

[2]FSBEI of Additional Professional Education "Russian Medical Academy of Continuous Professional Education" of the MH RF, Russia, Moscow, 2/1 Barrikadnaya str., buil. 1.

A case of a child with the breath-holding spells (BHS), atrioventricular block and long pauses of heart rhythm till 12 sec is presented. The attacks began at 1 year and completely stopped at 3 years. A typical ECG pattern for BHS is identified. The issues of therapy and the need for implantation of pacemaker are discussed.

Key words: breath-holding spells; atrioventricular block; children; arrhythmia in children; syncope; asystole; pacing

Conflict of Interest: none.
Funding: none.
Received: 23.08.2024 **Revision received:** 11.11.2024 **Accepted:** 21.11.2024
Corresponding author: Makarov Leonid, E-mail: dr.leonidmakarov@mail.ru

L.M.Makarov - ORCID ID 0000-0002-0111-3643, V.N.Komolyatova - ORCID ID 0000-0002-3691-7449, I.I.Kiseleva - ORCID ID 0000-0002-4867-0594, A.V.Dmitrieva - ORCID ID 0000-0002-0314-5235

For citation: Makarov LM, Komolyatova VN, Kiseleva II, Dmitrieva AV. Syncope, asystole and atrioventricular block in a child with breath-holding spells: a case report. *Journal of Arrhythmology.* 2024;31(4): e1-e6. https://doi.org/10.35336/VA-1396.

Syncope is a common occurrence in children [1]. According to the EPISODE study [2], up to 4% of Russian children have experienced episodes of syncope during their lifetime. The prognosis and management of a child with syncope are determined by identifying the specific mechanism underlying the event. We present a case involving a combination of syncope, prolonged asystole, and atrioventricular (AV) block in a young child.

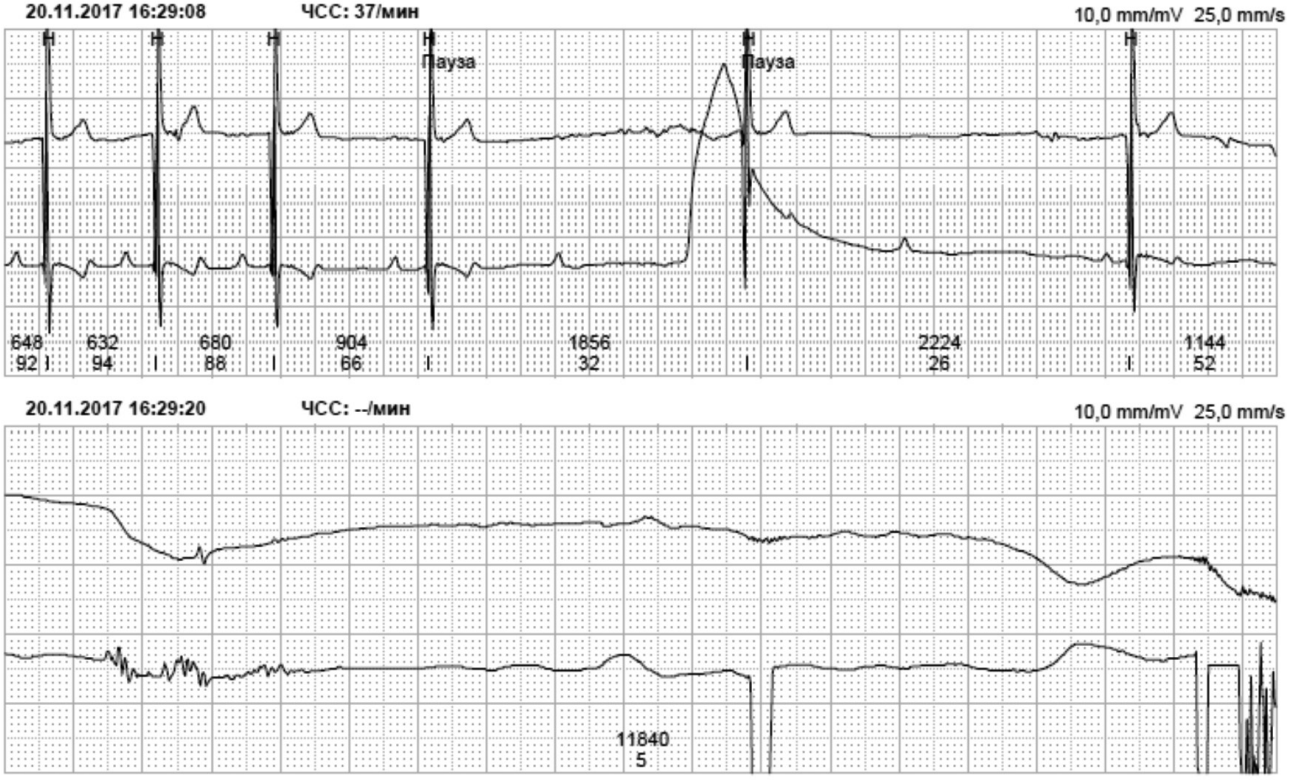

Figure 1. Child M., 1 year 6 months old (20.11.2017), at 16:29, during agitation and heart rate of 45 bpm, a sudden rhythm pause of 11,840 ms occurs, accompanied by loss of consciousness. During the pause, transient first-degree AV block with PR prolongation to 180 ms is observed, progressing to advanced AV block (top panel) and subsequent absence of atrial contractions as asystole prolongs (bottom panel).

Clinical case description

We observed a six-year-old child, M.D. The child was born at term from the third pregnancy and third full-term delivery, with two healthy siblings. The pregnancy and delivery were uncomplicated, and the child's development proceeded according to age. At the age of 1 year and 1 month, episodes of loss of consciousness began. These episodes occurred during the day and were consistently triggered by negative emotions or painful stimuli (e.g., a fall during play). During heightened emotional distress, the child would suddenly pale and "collapse" during inhalation. The syncope lasted up to one minute, with a frequency ranging from weekly to several times a day. There were no seizures during the episodes, although occasional involuntary urination was noted. The child recovered independently, with clear consciousness, recognizing the mother and surroundings immediately afterward, without drowsiness. Skin color returned from pale to normal pink.

The child was evaluated by a neurologist, and epilepsy was ruled out. Blood tests revealed no abnormalities, including no anemia. Holter monitoring (HM) conducted earlier recorded prolonged rhythm pauses of up to 8 seconds during these episodes. At the age of 1 year and 6 months, the child was referred to a cardiac surgery center, where hospitalization for pacemaker implantation was recommended. The following day (13 November 2017), the child's mother sought our consultation.

At the consultation, the child weighed 11.5 kg and measured 83 cm in height, with a proportional body structure. A primary physical examination revealed no abnormalities across systems, and there were no dysmorphic features. The heart's borders were normal, with no pathological murmurs. Blood pressure was 85/45 mmHg. A 12-lead electrocardiogram (ECG) showed a heart rate (HR) of 134 bpm, an electrical axis of 75°, a PR interval of 0.12 seconds, and a QT interval of 280 ms (QTc 395 ms). All ECG parameters were within the normal range for age [3]. Echocardiography showed no pathology, including no heart defects, cardiomyopathies, chamber dilation, or valvular abnormalities.

During HM (20 November 2017), two typical episodes were recorded while the child was awake and experiencing negative emotional reactions. These episodes began with increasing sinus tachycardia (150-160 bpm), progressing to brief rhythm slowing (62-34 bpm), first-degree AV block, and sinus node arrest lasting up to 11,840 ms (Fig. 1). Three additional clinical episodes without loss of consciousness were recorded, displaying similar ECG patterns with rhythm pauses of up to three seconds. Several episodes of transient first-degree AV block with a maximum PR interval of 0.3 seconds were also noted.

Based on the typical clinical presentation, the diagnosis was established as pallid-type breath-holding spells (BHS), cardioinhibitory variant. A comprehensive therapeutic regimen recommended for children with BHS was implemented [4-7], including piracetam (30-50 mg/kg/day), iron supplements (3 mg/kg/day) as advised regardless of anemia presence, belladonna, and beta-blockers (propranolol, 1 mg/kg/day) to prevent reflex syncope triggered by increasing sinus tachycardia [8]. However, clinical improvement was not achieved, leading to a decision to discontinue medication.

Repeated HM consistently demonstrated the same ECG changes during episodes, which we termed the "clinical-electrocardiographic pattern of BHS" (Fig. 2). Rhythm pauses were characterized by either a clean isoelectric line or a rhythm with episodes of atrial activity (second-degree AV block with 3:1 conduction, as seen in Fig. 1). Throughout the observation period, transient first- and occasionally second-degree AV block episodes were regularly recorded on HM. However, the duration of pauses during AV block was not associated with clinical manifestations of BHS.

Since no effect was achieved with the administered medical therapy, the necessity of implanting a pacemaker (PM) was repeatedly considered. However, the primary clinical symptom remained breath-holding spells (BHS), occurring at a typical age, leading us to conclude that the child's prognosis was generally favourable. The diagnosis of sick sinus syndrome (SSS) was ruled out based on the typical clinical presentation, asystole occurring only during wakefulness, the absence of nocturnal bradycardia, and high heart rates during the day.

Evaluating the opinions of leading experts on this issue, we noted that the question of pacemaker implantation regularly arises in children with BHS and prolonged asystole. This decision is made on an individual basis, depending on the treatment protocols adopted in a particular clinic, as well as the preferences of the parents and the

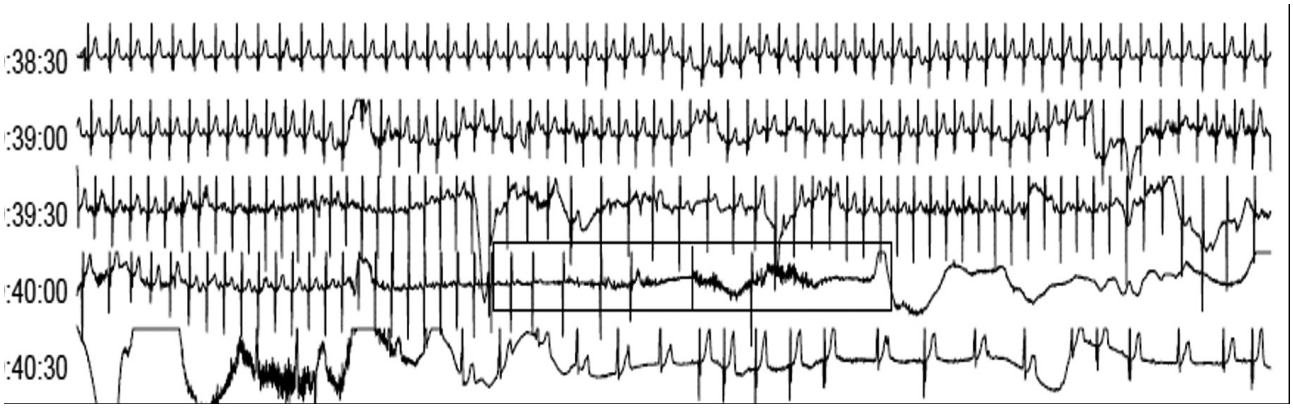

Figure 2. "Clinical and Electrocardiographic Pattern of BHS" in child M.D., 2 years and 3 months old, during Holter monitoring. A progressive sinus tachycardia develops in response to the child's negative emotional reaction, transitioning to a sharp rhythm deceleration during breath-holding and a prolonged pause (highlighted in rectangle), leading to syncope and subsequent gradual spontaneous rhythm recovery.

attending physician [9-13]. Based on our own experience with children with BHS and the recommendations of the European Society of Cardiology on syncope management [1], we opted against PM implantation.

At the age of 3 years, the patient's episodes completely ceased. During the latest examination (17 July 2024), when the child was 6 years old, the following ECG parameters were recorded: heart rate (HR) of 110 bpm (normal up to 105 bpm), an electrical axis of 78°, PR interval of 0.18 seconds (normal up to 0.14 seconds), and a QTc interval of 435 ms using Bazett's formula (normal up to 440 ms) and 393 ms using Fridericia's formula (normal up to 430 ms) [3]. Holter monitoring (17 July 2024) showed a mean 24-hour HR of 90 bpm (normal 79-91 bpm) with a normal circadian rhythm profile (circadian index of 1.31). Almost continuously (except during sinus tachycardia with an HR above 125-130 bpm), first-degree AV block was recorded, with a maximum PR interval of 0.3 seconds during the night.

During nocturnal sleep, there were 209 episodes of second-degree AV block, Mobitz type I, with a maximum rhythm pause of 1981 ms (Fig. 3). At peak heart rates, AV conduction was intact, with a PR interval of 0.12-0.13 seconds. The average daily QTc interval was within normal limits (429 ms). Heart rate variability was moderately reduced.

We consider the prognosis for this child regarding the development of life-threatening bradyarrhythmias to be favourable without PM implantation. However, continued monitoring is essential given the persistence and moderate progression of the AV block. During follow-up, it is necessary to exclude conditions associated with progressive conduction system disorders (e.g., by analysing family history and performing serial ECG assessments of the patient and family members). No medication is currently prescribed.

DISCUSSION

Breath-holding spells, classified under ICD-10 code R06, occur in early childhood and are characterised by sudden cessation of breathing, often accompanied by loss of consciousness and, occasionally, seizures. BHS typically develop in response to negative emotional stimuli or painful irritation. In neurology, BHS are categorised as "generalised tonic or tonic-clonic paroxysms of a non-epileptic nature." The term has numerous synonyms, including reflex anoxic seizures, non-epileptic vagal attacks, anoxo-asphyxial seizures, and affective-respiratory paroxysms [1, 4, 9, 14, 15].

The prevalence of BHS in the population varies, but most sources cite a frequency of up to 5% [14, 15]. Episodes typically begin between 6 and 18 months of age [15]. Less than 10% of cases develop after the age of 2 years. The frequency of episodes ranges from daily to once a year, but most children experience one to six episodes per week [9, 15]. The incidence of BHS tends to decrease with age: by 4 years, 50% of children no longer experience BHS, and episodes generally cease by the age of 8 [9, 10, 14, 15].

BHS are classified into "blue" and "pale" types based on skin colour changes during episodes. Cyanotic episodes ("blue" BHS) are more common, occurring in 52% of cases, while 28% of children are diagnosed with the "pale" type, and the remainder exhibit mixed features [9]. Prolonged rhythm pauses are characteristic of the "pale" type, usually triggered by sudden fear, pain, falls, or minor injuries [9, 15]. The occurrence of asystole in this variant is associated with a reflexive increase in the vagal sensitivity of the sinus node [14, 15]. Nearly all children with the pale variant of BHS exhibited asystole lasting over 20 seconds during the Aschner test, an effect absent in the control group and eliminated with atropine administration [15].

Long-term follow-up of 70 children with BHS by D.D. Korostovtsev [15] revealed no association between BHS and sudden death. Thirty-five children were monitored into adolescence (ages 7-12 years). While prolonged asystole of 20 seconds or more was noted in cases of the pale variant, none of the children experienced sudden death. Intellectual and psychological development of children with BHS did not differ from that of the control group, indicating that frequent syncopal episodes and asystole do not result in chronic cerebral hypoxia.

Long-term follow-up of children with early-life BHS showed that 60-75% may develop asthenic syndrome, 10-15% suffer from hysterical neuroses and sleep disturbances, and up to 10% experience reflex syncope and migraines. Only 2.4% of children with epilepsy had a history of BHS [15]. We monitored 14 children with a full clinical presentation of BHS and another 13 with a preschool history of BHS. None required pacemaker implantation, and all exhibited a favourable prognosis, with symptoms resolving by 6-7 years of age [16].

The cornerstone of BHS therapy is parental education, ensuring parents understand the benign nature of these episodes and the normal intellectual development of

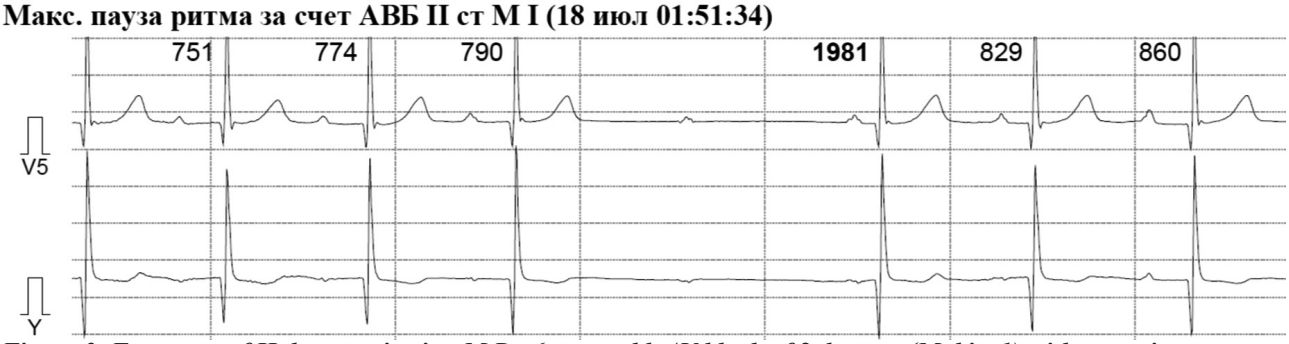

Figure 3. Fragment of Holter monitoring M.D., 6 years old. AV block of 2 degrees (Mobitz 1) with a maximum rhythm pause of 1981 ms.

their child [15, 17]. There is no standardised pharmacological treatment for BHS; however, several studies and guidelines suggest the effectiveness of certain methods. Commonly recommended treatments include piracetam, belladonna preparations, iron supplements (regardless of serum iron levels), and vagolytics [4-7]. Children with BHS are consistently monitored by neurologists and rarely raise concerns about life-threatening risks, as syncopal episodes always resolve spontaneously, even in cases of prolonged asystole and apnoea.

With the increasing use of HM in the evaluation of children with BHS, cardiologists have questioned whether prolonged pauses in heart rhythm in BHS increase the risk of sudden death and whether pacemaker implantation (PI) is necessary. From a traditional arrhythmology perspective, symptomatic asystole associated with loss of consciousness is an unequivocal indication for PI as a means to prevent sudden death in children [18]. However, this approach is justified in cases of true sinus node dysfunction or AV block of organic origin. In children with BHS, the "positive" effects of such therapy have been periodically reported, including a reduction in the frequency and duration of syncope [19-21].

On the other hand, S. Sartori [22], analysing 47 publications on the effectiveness of PI in children with BHS, demonstrated that while PI significantly reduces the duration of asystole in such cases, it is associated with technical issues in 25.7% of cases and medical complications in 11.4%. Importantly, no evidence was found linking BHS to sudden death. Although sudden deaths in children with BHS have been reported, they were attributable to other causes, including long QT syndrome, postoperative tracheoesophageal fistula, spindle-shaped dilation of the upper oesophagus, bronchopneumonia, progressive cerebral atrophy, brain glioma, and craniofacial malformations such as cleft palate [23, 24].

Recommendations to implant a pacemaker may appeal to parents and family members distressed by the frequent and seemingly "endless" severe paroxysms their child experiences. However, the European Guidelines on the Management of Syncope specify that BHS are classified as reflex syncope specific to infancy and childhood. Even in the presence of prolonged asystole, pacemaker implantation should be avoided due to the transient nature of these episodes and the favourable prognosis [1]. Similarly, we believe it is unjustifiable to implant a permanent pacing system in a child aged 1-3 years, given the high likelihood of resolution of non-life-threatening episodes within a few years and the potential complications associated with PI in this age group. We found no documented cases of lead extraction in children after the resolution of BHS.

The complexity of our case lies in the presence of a mildly progressive AV block, which is atypical for isolated BHS. While we cannot rule out its progression to symptomatic stages requiring PI in the future, this underscores the necessity for dynamic follow-up and further investigations to exclude conditions associated with progressive conduction system disease. Nevertheless, we firmly believe that PI was not indicated during the manifestation period of BHS in this child.

CONCLUSION

1. Asystole occurring during "pale" type breath-holding spells is not indicative of sinus node dysfunction. It is transient, prognostically benign, and does not warrant pacemaker implantation, regardless of the duration of asystole or the presence of syncope.
2. The clinical and electrocardiographic pattern of "pale" type BHS includes progressive sinus tachycardia triggered by the child's negative emotions or painful stimuli, abruptly interrupted by bradycardia transitioning into asystole, leading to syncope and sudden pallor of the skin.

REFERENCES

1. Brignole M, Moya A, de Lange JF, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J.* 2018; 39(21): 1883-1948. https//doi.org/10.1093/eurheartj/ehp298.
2. Makarov LM, Lesnitskaya MG, Komoliatova VN, Kiseleva II. The prevalence of loss of consciousness in children of school age. *Health care of the Russian Federation.* 2020;64(4): 190-195. (In Russ.). https://doi.org/10.46563/0044-197X-2020-64-4-190-195
3. Makarov LM, Kiseleva II, Komolyatova VN, Fedina NN. New standards and interpretations of children electrocardiogram. *Pediatria n.a. G.N. Speransky.* 2015; 94(2) (In Russ.).
4. Dai AI, Demiryürek AT. Effectiveness Oral Theophylline, Piracetam, and Iron Treatments in Children with Simple Breath-Holding Spells. *J Child Neurol.* 2020;35(1): 25-30. https//doi.org/10.1177/0883073819871854.
5. Leung AKC, Leung AAM, Wong AHC, Hon KL. Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence. *Curr Pediatr Rev*. 2019;15(1): 22-29. https//doi.org/10.2174/1573396314666181113094047.
6. Williams J, Cain N. Case report of successful treatment of pallid breath-holding spells with glycopyrrolate. *Pediatrics*. 2015;135(5): e1308-11. https//doi.org/10.1542/peds.2014-2456.
7. Gonzalez Corcia MC, Bottosso A, et al. Efficacy of treatment with belladonna in children with severe pallid breath-holding spells. *Cardiol. Young.* 2018;28(7): 922-927. https//doi.org/10.1017/S1047951118000458.
8. Balaji S, Oslizlok PC, Allen MC, et al. Neurocardiogenic syncope in children with a normal heart. *J Am Coll Cardiol.* 1994;23(3): 779-85. https//doi.org/10.1016/0735-1097(94)90768-4.
9. DiMario FJ. Breath-holding spells in childhood. *Am J Dis Child.* 1992;146(1): 125-31. https//doi.org/10.1001/archpedi.1992.02160130127035.
10. Bhatia MS, Singhal PK, Dhar NK, et al. Breath holding spells: an analysis of 50 cases. *Indian Pediatr.* 1990;27(10): 1073-9.
11. Wilson D, Moore P, Finucane AK, Skinner JR. Cardiac pacing in the management of severe pallid breath-holding attacks. *J Paediatr Child Health.* 2005;41(4): 228-30. https//doi.org/10.1111/j.1440-1754.2005.00594.x.
12. McLeod KA, Wilson N, Hewitt J, et al. Cardiac pacing for severe childhood neurally mediated syncope with reflex anoxic seizures. *Heart.* 1999;82(6): 721-5. https//doi.

org/10.1136/hrt.82.6.721.
13. Kelly AM, Porter CJ, McGoon MD, et al. Breath-holding spells associated with significant bradycardia: successful treatment with permanent pacemaker implantation. *Pediatrics*. 2001;108(3): 698-702. https//doi.org/10.1542/peds.108.3.698.
14. Stephenson JB. Reflex anoxic seizures ('white breath-holding'): nonepileptic vagal attacks. *Arch Dis Child.* 1978;53(3): 193-200. https//doi.org/10.1136/adc.53.3.193.
15. Korostovtsev D.D. Affective-respiratory seizures. In: Guzeva V.I. Epilepsy and non-epileptic paroxysmal conditions in children. - M: OOO "Medical Information Agency". 2007; pp. 527-533. (In Russ.) ISBN: 5-89481-533-9
16. Makarov LM, Komolatova VN. Cardiological aspects of breath-holding spells and the risk of SCD. In: Makarov L.M., Komolatova V.N. (eds.). In: Sudden cardiac death in children, adolescents and young people. - M .: ID "Medpraktika - M, 2021. pp. 108-118 (In Russ.) ISBN 978-5-98803-446-9.
17. Haverkamp F, Noeker M. Traditional view empirically revisited: normal intellectual functioning in breath holding spells. *Eur J Pediatr.* 1998;157(4): 354. https//doi.org/10.1007/s004310050829.
18. Revishvili ASh, Boytsov SA, Davtyan KV, et al. Clinical recommendations for conducting electrophysiological studies, catheter ablation and the use of implantable antiarrhythmic devices of the All-Russian Scientific Society of Arrhythmologists. Moscow 2017, p. 45. (In Russ.) ISBN 978-5-9500922-0-6.
19. Sreeram N, Whitehouse W. Permanent cardiac pacing for reflex anoxic seizure. *Arch Dis Child.* 1996;75(5): 462. https//doi.org/10.1136/adc.75.5.462.
20. Kelly AM, Porter CJ, McGoon MD, et al. Breath-holding spells associated with significant bradycardia: successful treatment with permanent pacemaker implantation. *Pediatrics.* 2001;108(3): 698-702. https//doi.org/10.1542/peds.108.3.698.
21. Wilson D, Moore P, Finucane AK, Skinner JR. Cardiac pacing in the management of severe pallid breath-holding attacks. *J Paediatr Child Health.* 2005;41(4): 228-30. https//doi.org/ 10.1111/j.1440-1754.2005.00594.x.
22. Sartori S, Nosadini M, Leoni L, et al. Pacemaker in complicated and refractory breath-holding spells: when to think about it? *Brain Dev.* 2015;37(1): 2-12. https//doi.org/10.1016/j.braindev.2014.02.004.
23. Robinson JA, Bos JM, Etheridge SP, Ackerman MJ. Breath Holding Spells in Children with Long QT Syndrome. *Congenit Heart Dis.* 2015;10(4): 354-61. https//doi.org/ 10.1111/chd.12262.
24. Southall DP, Samuels MP, Talbert DG. Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death. *Arch Dis Child*. 1990;65(9): 953-61. https//doi.org/10.1136/adc.65.9.953.

https://doi.org/10.35336/VA-1365

MULTIPURPOSE APPROACH TO THE TREATMENT OF CHRONIC HEART FAILURE: IMPLANTATION OF SYSTEM SUBCUTANEOUS CARDIOVERTER-DEFIBRILLATOR AND CARDIAC CONTRACTILITY MODULATION DEVICE. A CASE REPORT

V.A.Amanatova[1], T.M.Uskach[1, 2], I.R.Grishin[1], A.V.Vereshchagina[1], A.A.Safiullina[1], O.V.Sapelnikov[1], S.N.Tereshchenko[1, 2]

[1]FSBI "NMRC of Cardiology named after acad. E.I.Chazov" of the MH RF, Moscow, 15A Academician Chazov str.;
[2]FSBEI APE "Russian Medical Academy of Continuous Professional Education" of the MH RF, Moscow, 2/1 Barrikadnaya str., buil. 1.

A clinical case of patient with implanted system subcutaneous cardioverter-defibrillator and cardiac contractility modulation device is described. No violations were identified in the joint operation of the devices.

Key words: subcutaneous cardioverter-defibrillator system; primary prevention of sudden cardiac death; chronic heart failure; cardiac contractility modulation.

Conflict of Interest: none.
Funding: none.
Received: 30.05.2024 **Revision received:** 08.11.2024 **Accepted:** 28.11.2024
Corresponding author: Amanatova Valeria, E-mail: amanatova.v@yandex.ru

V.A.Amanatova - ORCID ID 0000-0002-0678-9538, T.M.Uskach - ORCID ID 0000-0003-4318-0315, I.R.Grishin - ORCID ID 0000-0002-2689-2751, A.V.Vereshchagina - ORCID ID 0000-0001-8158-3794, A.A.Safiullina - ORCID ID 0000-0003-3483-4698, O.V.Sapelnikov - ORCID ID 0000-0002-5186-2474, S.N.Tereshchenko - ORCID ID 0000-0001-9234-6129

For citation: Amanatova VA, Uskach TM, Grishin IR, Vereshchagina AV, Safiullina AA, Sapelnikov OV, Tereshchenko SN. Multipurpose approach to the treatment of chronic heart failure: implantation of system subcutaneous cardioverter-defibrillator and cardiac contractility modulation device. A case report. *Journal of Arrhythmology.* 2024;31(4): e7-e13. https://doi.org/10.35336/VA-1365.

Chronic heart failure (CHF) with reduced left ventricular ejection fraction (LVEF) is characterized by a steadily progressive course. Despite the diversity and efficacy of medical therapy, surgical intervention is often required for these patients. Individuals with CHF are at a high risk of sudden cardiac death (SCD). In the general population, the majority of CHF patients belong to functional class II, where SCD remains the leading cause of death, according to research data[1, 2]. Additionally, the risk of SCD is significantly higher among patients with coronary artery disease.

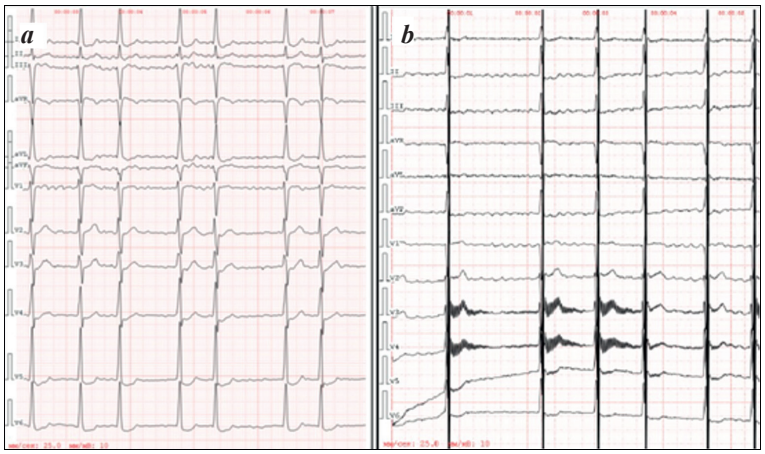

Fig. 1. Patient's ECG after implantation of the CCM device: without CCM therapy (a) and during CCM therapy delivery (b).

To prevent SCD, both primary and secondary, the implantation of an implantable cardioverter-defibrillator (ICD) is commonly employed [3]. Until recently, transvenous ICD systems were the sole option available. In these systems, the defibrillation lead is endocardial, delivered via the subclavian and superior vena cava into the right ventricle, where it is anchored at the apex. However, the transvenous placement of these system components can lead to various complications, such as thrombosis and occlusion of major vessels, fractures of endocardial leads, worsening of tricuspid valve insufficiency, and infectious complications. These issues often necessitate serious interventions, including complete extraction of the ICD system [4].

As an alternative to transvenous ICDs, subcutaneous ICD (S-ICD) systems can be offered to patients. This device has been available in the Russian Federation since 2016. Subcutaneous systems are designed for younger patients, those who do not require antibradycardia or antitachycardia pacing, or resynchronization therapy[5, 6]. The implantation of S-ICDs is associated with a lower incidence of infectious complications. Moreover, due to the absence of intracardiac components, there is no impairment of tricuspid valve function compared to trans-

venous ICD systems, even in the presence of other implanted devices[5–8].

A significant proportion of CHF patients have a normal QRS complex duration, precluding the use of resynchronization therapy for their treatment[9]. Currently, a technique known as cardiac contractility modulation (CCM) is available for patients with CHF, reduced LVEF, and narrow QRS complexes[10, 11]. This treatment involves the implantation of a device consisting of an implantable pulse generator and two ventricular leads anchored in the interventricular septum. The implantation technique is like that for standard pacemakers or transvenous ICDs. The device delivers high-amplitude stimulation during the absolute refractory period of ventricular depolarisation, which does not trigger subsequent contraction. Consequently, the CCM device does not affect heart rhythm. This stimulation increases phospholamban phosphorylation, thereby raising calcium levels in cardiomyocytes, ultimately enhancing myocardial contractility[11, 12].

Experience with the combined use of S-ICD systems and CCM devices in the global literature is limited, which prompted the consideration of this clinical case.

Clinical case description

A 51-year-old patient with CHF and reduced left LVEF, accompanied by atrial fibrillation (AF). The medical history included hypertension diagnosed in 2002 and type 2 diabetes mellitus diagnosed in 2005. In 2012, the patient presented with symptoms of exertional angina, and coronary angiography revealed a haemodynamically significant stenosis of up to 90% in the left anterior descending artery. Percutaneous transluminal coronary angioplasty with stenting was performed.

In 2015, symptoms of exertional angina recurred, leading to coronary angiography and angioplasty of the circumflex artery due to significant stenosis. In 2018, the patient experienced the first paroxysm of AF, with a noted reduction in LVEF to 29%. CHF was diagnosed, and therapy was initiated. In 2019, in-stent restenosis was detected in the left anterior descending artery, which required endovascular intervention. In September 2020, the patient was hospitalised with complaints of exertional dyspnoea.

At admission, the patient was on comprehensive CHF therapy, including valsartan/sacubitril, bisoprolol, furosemide, digoxin, eplerenone, rivaroxaban, atorvastatin, and empagliflozin, alongside medications for comorbidities. The admission ECG showed AF with a ventricular rate of 72–135 bpm and a QRS complex duration of 100 ms. Blood tests revealed an NT-proBNP level of 4217 pg/mL.

Transthoracic echocardiography (TTE) indicated significant chamber dilation, including a left atrial volume of 219 mL with an indexed volume of 91.3 mL/m². The left ventricular myocardium demonstrated reduced contractile function (LVEF 26%) without clearly defined zones of regional wall motion abnormalities. Given the history of extensive coronary artery disease and to exclude post-infarction myocardial fibrosis while evaluating myocardial perfusion, scintigraphy with 99mTc-MIBI at rest was performed. The study revealed small focal perfusion defects

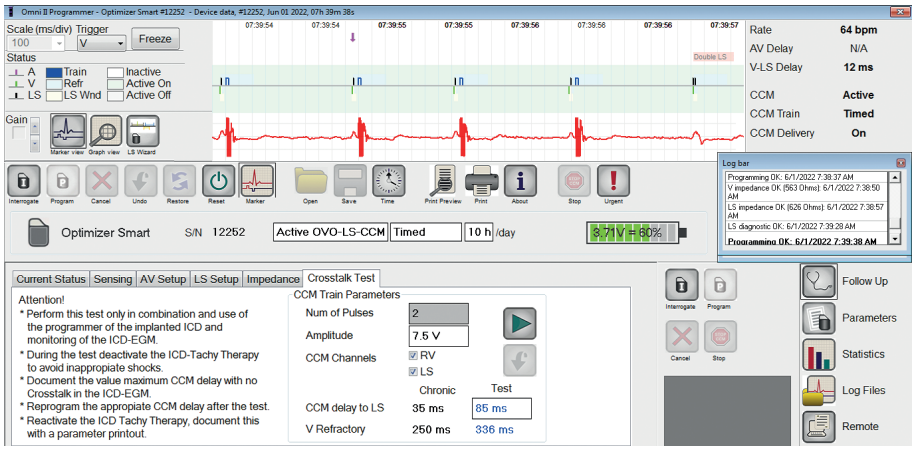

Fig. 2. Cross-talk testing: programmer data.

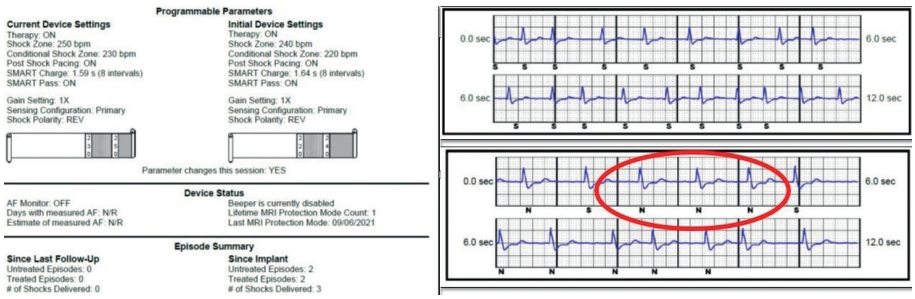

Fig. 3. Programmer data from the subcutaneous ICD system: absence of double counting of CCM therapy signals.

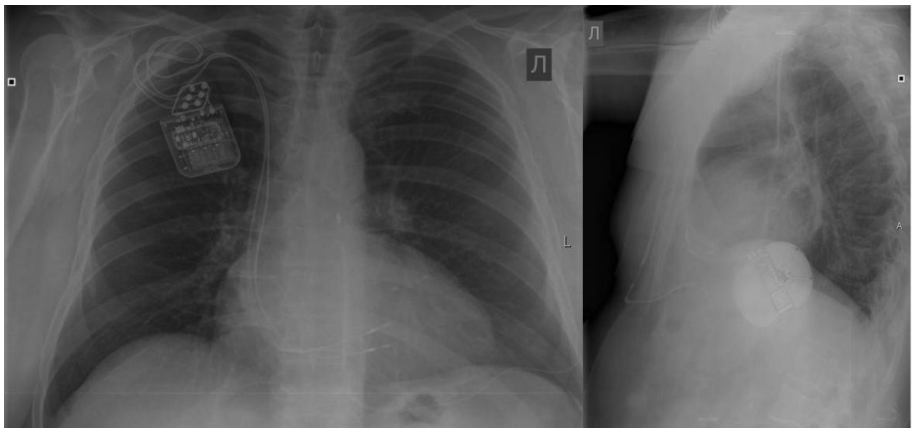

Fig. 4. Chest X-ray of the patient after implantation of the CCM device and subcutaneous ICD system.

in the apex, portions of the apical and mid-anterior wall segments, and basal segments of the inferior wall, totalling 10–12% of the left ventricular surface area, alongside significantly reduced left ventricular contractility.

Considering the diagnosis of coronary artery disease and CHF with reduced LVEF, despite optimal medical therapy for over three months, the patient was indicated for ICD implantation as primary prevention of SCD. Given the patient's relatively young age, lack of indication for antibradycardia or antitachycardia pacing, and the absence of a need for cardiac resynchronisation therapy, a subcutaneous ICD system was implanted.

In April 2021, the patient contracted COVID-19. By May 2021, they reported worsening dyspnoea and the development of oedema in the feet and lower legs. They were rehospitalised with decompensated CHF involving both systemic and pulmonary circulations. Aggressive diuretic therapy was administered, but the patient experienced severe hypotension (70/40 mmHg) and a reduced urine output. Dobutamine and noradrenaline therapy were initiated, leading to stabilisation of their condition. Echocardiography showed a further decrease in LVEF to 25%.

The patient was discharged with recommendations for close follow-up. After three months, LVEF remained reduced at 25%, and no shock therapy events were recorded during ICD checks. The lack of improvement indicated the need for CCM therapy. Given the satisfactory perfusion in all interventricular septal segments, as shown by myocardial scintigraphy, electrodes were implanted in the upper and middle thirds of the interventricular septum, an optimal choice for CCM electrode placement. Figure 1 illustrates the functionality of the CCM device recorded during a standard resting 12-lead ECG.

Intraoperative testing included cross-talk assessments to exclude interference between the CCM device and the ICD. Such interference could lead to misinterpretation of CCM impulses as ventricular tachycardia or fibrillation, potentially triggering inappropriate ICD shock therapy (Fig. 2). No cross-talk was observed during ICD testing (Fig. 3). Figure 4 shows a chest X-ray of the patient after the implantation of both devices.

Six months after the CCM device implantation, a follow-up echocardiogram showed an improvement in LVEF from 25% to 35%, with reductions in cardiac chamber sizes: left ventricular end-diastolic volume decreased by 43%, end-systolic volume by 53%, and left atrial volume by 8%. NT-proBNP levels decreased more than tenfold, to 325.3 pg/mL.

However, six months after treatment, the patient reported an ICD shock. Device interrogation revealed an episode of atrial fibrillation with rapid ventricular response (Figure 5), during which shock therapy was delivered. The ICD parameters were adjusted, and the beta-blocker dose was increased.

DISCUSSION

Currently, interventional treatment methods are widely employed in clinical practice for managing CHF, alongside pharmacotherapy. Device implantation plays a crucial role in improving patient prognosis. With increased life expectancy and advancements in CHF treatment, the number of patients requiring multiple implanted devices is rising. However, there is limited data on the interaction between different devices. The presence of multiple intracardiac leads may increase the risk of complications.

In the presented clinical case, the patient had indications for both CCM and ICD implantation. At present, no device combines CCM therapy and ICD functions into a single system. According to clinical guidelines, patients with CHF who are not candidates for cardiac resynchronisation therapy (CRT) require ICD implantation for the prevention of SCD. Additionally, CCM device implantation may be considered to improve patient outcomes, as recommended in CHF management guidelines. Subcutaneous ICD (S-ICD) implantation is preferred for patients with pre-existing CCM devices to minimise the risk of complications associated with more than two intracardiac leads. There are only a few documented cases of such combinations in the literature. These cases highlight the issue of potential interference between the two implanted devices and strategies to prevent cross-talk, wherein CCM signals could be misinterpreted by the ICD as ventricular arrhythmias, triggering inappropriate shockslo-

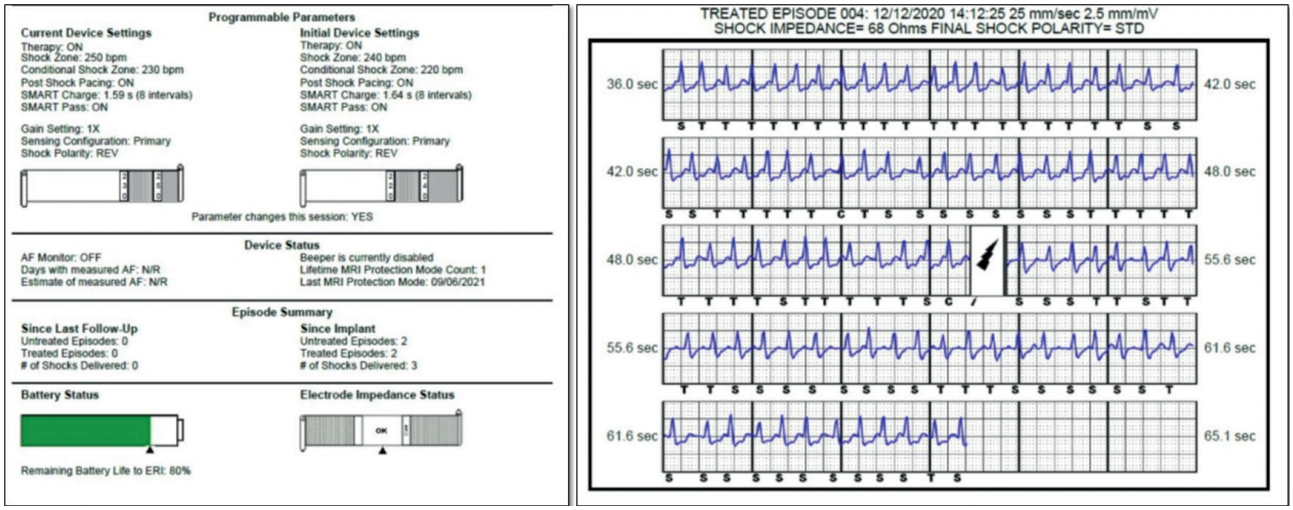

Fig. 5. Programmer data from the subcutaneous ICD system: segment showing shock delivery during tachysystolic AF.

cal study reported on 20 patients with CCM and S-ICD devices. All patients underwent intraoperative cross-talk testing to rule out interference between the implanted systems. This standardised procedure involved simultaneous activation of both devices to assess the QRS configuration and the CCM device's spikes as detected by the S-ICD. Various CCM stimulation delays and durations were temporarily programmed. The mean follow-up duration was 34.3 months. Functional class improved significantly from 2.9±0.4 to 2.1±0.7 ($p<0.0001$), and quality of life scores improved from 50.2±23.7 to 29.6±22.8 points on the Minnesota Living with Heart Failure Questionnaire ($p<0.0001$). LVEF increased from 24.4±8.1% to 30.9±9.6% ($p=0.002$). Over an average 22-month observation period with both devices active, three patients experienced a total of six episodes of sustained ventricular tachycardia, all successfully treated by the ICD's first shock. No damage or dysfunction of the CCM device was observed during defibrillation. One patient received an inappropriate ICD shock unrelated to CCM therapy, and another underwent explantation of both devices after receiving a mechanical circulatory support device .

As demonstrated rience and the limited international data available, interference between the devices does not occur. The S-ICD, like its transvenous counterpart, incorporates arrhythmia discrimination algorithms. Notably, the CCM device automatically halts therapy delivery when the ventricular rate exceeds 110 bpm, as per its programmed settings, reducing the likelihood of interference in cases of atrial fibrillation with rapid ventricular response.

Algorithms for discrimination of subcutaneous ICD arrhythmias

One of the auxiliary tools in the device's logic for accurately identifying arrhythmias is the SMART Pass function. This feature activates an additional high-frequency filter that reduces oversensing while maintaining an adequate sensing margin. Notably, SMART Pass has been shown to reduce the number of inappropriate therapies by over 40%. This function is activated when the measured ECG signal amplitude during configuration is at least 0.5 mV. The device continuously monitors signal amplitude and deactivates SMART Pass if sensing inadequacy is suspected [15].

The device prevents inappropriate therapy by recognizing noise and avoiding multiple counting of individual cardiac cycles. This is achieved through automatic signal analysis that includes detection, event certification, and decision-making phases. During the detection phase, the device uses a detection threshold to identify events. This threshold is continuously and automatically adjusted based on the amplitude of recently detected electrical events. The device also modifies parameters to enhance sensitivity for detecting fast rhythms. Events identified in the detection phase are examined in the certification phase, where they are classified as certified cardiac events or suspected artifacts (e.g., muscle activity or external signals) [15].

In the subcutaneous ICD system, two programmable tachycardia zones are available: the "Charge Zone" and the "Conditional Shock Zone." In the "Charge Zone," heart rate is the sole criterion used to determine the need for electrical shock therapy. In the "Conditional Shock Zone," additional parameters, such as heart rate and morphology, are analyzed to evaluate the appropriateness of delivering therapy. This zone differentiates treatable events from others, such as AF, sinus tachycardia, or supraventricular tachycardias.

A reference template of the normal sinus rhythm (NSR) is created during device initialization. This NSR template is used in the "Conditional Shock Zone" to identify treatable arrhythmias. In addition to morphology comparison with the NSR template, the device conducts other morphological analyses to detect polymorphic rhythms. The morphology and QRS complex width are used to identify monomorphic arrhythmias, such as ventricular tachycardia. If the "Conditional Shock Zone" is enabled, arrhythmias are considered treatable according to a decision-making algorithm (Figure 6) [15].

For patients with paroxysmal AF, the device also features an AF Monitor function, which alerts clinicians to AF episodes lasting at least six minutes within a day. These six minutes can consist of a single episode or several shorter ones. AF detection relies on groups of 192 peaks, with at least 80% of the peaks in a group needing to indicate AF for the group to be counted. Consequently, the AF Monitor function may underestimate total AF duration in cases of certain arrhythmia types or brief episodes[15].

All the algorithms aim to minimize inappropriate shocks, which is particularly crucial when used alongside a CCM device. To avoid cross-talk between CCM therapy signals and intrinsic QRS complexes, intraoperative cross-talk testing is necessary. Additionally, if CCM signals are detected by the subcutaneous ICD, adjustments can be made to stimulation amplitude, the number of CCM therapy impulses, or the daily duration of CCM stimulation to ensure adequate stimulation percentages.

In the presented case, an episode of AF with tachysystole was within the "Shock Zone," leading to an inappropriate device discharge. Conducting a telemetry assessment of the device and reprogramming the subcutaneous ICD prevented further inappropriate shocks. Post-defibril-

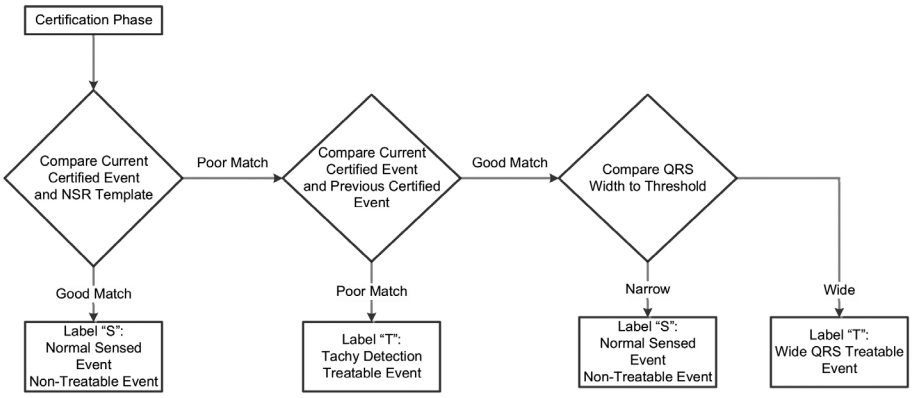

Fig. 6. Decision-making scheme for shock therapy delivery, illustrating the device's internal logic. Adapted from [15].

lation checks of the CCM device revealed no disruptions in its function. No interactions between the two devices that could impair their operation were observed. Thus, with proper monitoring and timely adjustments of modern CHF treatment devices, patients can receive the necessary therapy without adverse effects or diminished quality of life.

CONCLUSION

Modern treatment of chronic heart failure is inseparable from the use of interventional methods that extend patient survival and improve quality of life. The simultaneous use of multiple devices necessitates precise indication determination and careful monitoring to ensure their safe interaction. This clinical case illustrates the feasibility of combining implantable cardioverter-defibrillator and cardiac contractility modulation systems in a patient with CHF and atrial fibrillation. The global accumulation of experience with complex device implantation continues to grow. Advances in device management techniques will enable the application of non-pharmacological treatments for CHF in a broader range of patient categories in the future.

REFERENCES

1. Santangeli P, Rame JE, Birati EY, Marchlinski FE. Management of Ventricular Arrhythmias in Patients With Advanced Heart Failure. *J Am Coll Cardiol.* 2017;69(14): 1842-1860. https://doi.org/10.1016/j.jacc.2017.01.047.
2. Wong CX, Brown A, Lau DH, et al. Epidemiology of Sudden Cardiac Death: Global and Regional Perspectives. *Heart Lung Circ.* 2019;28(1): 6-14. https://doi.org/10.1016/j.hlc.2018.08.026.
3. 2020 Clinical practice guidelines for chronic heart failure. *Russian Journal of Cardiology*. 2020;25(11): 4083. (In Russ.). https://doi.org/10.15829/1560-4071-2020-4083.
4. Aivazyan SA, Sapelnikov OV, Grishin IR, Sorokin IN. Risk stratification scales for extraction of electrodes in cardiac implantable electronic devices and prospects for their practical application: a review of the literature. *Journal of arrhythmology.* 2022;29(2): 50-57 (In Russ.). https://doi.org/10.35336/VA-2022-2-05.
5. Vereshchagina AV, Uskach TM., Sapelnikov OV, et al. Safety and Tolerability of Implanted Subcutaneous Cardioverter-defibrillator Systems. *Rational Pharmacotherapy in Cardiology.* 2022;18(4): 427-432 (In Russ.). https://doi.org/10.20996/1819-6446-2022-08-05.
6. Vereshchagina AV, Uskach TM, Sapelnikov OV, et al. Preimplantation screening of patients-candidates for implantation of a subcutaneous cardioverter-defibrillator: predictors of the outcomes. *Russian Cardiology Bulletin.* 2021;16(4): 58-65. (In Russ.). https://doi 10.17116/Cardiobulletin20211604158.
7. Prokopenko AV, Ivanitskiy EA. Subcutaneous cardioverter-defibrillator, patient selection, implantation, postoperative management in the Krasnoyarsk. *Russian Journal of Cardiology*. 2022;27(8): 104-108. https://doi 10.15829/1560-4071-2022-5116.
8. Prokopenko AV, Ivanitskiy EA. Experience of the using of subcutaneous cardioverter-defibrillators in the world practice: review. *Journal of Arrhythmology.* 2022;29(4): 42-46 (In Russ.). https://doi.org/10.35336/VA-2022-4-06.
9. Lund LH, Jurga J, Edner M, et al. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *Eur Heart J.* 2013;34(7): 529-39. https://doi.org/ 10.1093/eurheartj/ehs305.
10. Davtyan KV, Mironova NA, Chugunov IA, et al. Cardiac contractility modulation therapy in patients with implanted cardiac resynchronization therapy: results of the 2 year follow-up. *Journal of Arrhythmology.* 2023;30(3): 16-22 (In Russ.). https://doi. org/10.35336/VA-1145.
11. Uskach TM, Sapelnikov OV, Safiullina AA, et al. Implantation of a cardiac contractility modulator in chronic heart failure and atrial fibrillation: results of a 6-month follow-up of one hundred patients. *Russian Journal of Transplantology and Artificial Organs.* 2021;23(1): 30-37 (In Russ). https://doi.org/10.15825/1995-1191-2021-1-30-37.
12. Lyasnikova EA, Sukhareva KS, Vander MA, et al. Molecular effects of cardiac contractility modulation in patients with heart failure of ischemic aetiology uncovered by transcriptome analysis. *Frontiers in Cardiovascular Medicine.* 2024;11: 1321005. https://doi.org/10.3389/fcvm.2024.1321005.
13. Yao J, Gao J, Yan J-F, Fang S. Cardiac contractilitymodulation and subcutaneous defibrillator (S-ICD): First experience with simultaneous implantation. *Pacing Clin Electrophysiol.* 2023;1-4. https://doi.org/10.1111/pace.14695.
14. Röger S, Rudic B, Akin I, et al. Long-term results of combined cardiac contractility modulation and subcutaneous defibrillator therapy in patients with heart failure and reduced ejection fraction. *Clin Cardiol.* 2018;41(4): 518-524. https://doi.org/10.1002/clc.22919.
15. User Manual EMBLEM S-ICD, EMBLEM MRI S-ICD. Subcutaneous implantable cardioverter defibrillator. Available from: https://www.bostonscientific.com/content/dam/elabeling/crm/92346913-027_EMBLEM-_S-ICD_UM_en_S.pdf.

https://doi.org/10.35336/VA-1356

CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH SYSTOLIC LEFT VENTRICULAR DYSFUNCTION

R.D.Khuziakhmetov[1], E.A.Shishkina[2], B.K.Kadyraliev[1], V.A.Belov[1], S.N.Azizov[1], O.V.Khlynova[2]

[1]FSBI "Federal Center of Cardiovascular Surgery named after S.G. Sukhanov" of the MH RF, Russia, Perm, 35 Marshal Zhukov str; [2]FSBIHI "Academician E.A. Vagner Perm State Medical University" of the MH RF, Russia, Perm, 26 Petropavlovskaya str.

Atrial fibrillation (AF) is the most common arrhythmia among the adult population, affecting up to 2% of the population. Among patients with chronic heart failure (CHF), the prevalence of AF reaches 12.3%. The presence of common risk factors and pathophysiological mechanisms of AF and CHF development lead to the frequent combination of these two pathologies, which has a negative impact on the course of the underlying disease and further prognosis, increasing the chances of adverse outcomes such as stroke, myocardial infarction, and cardiovascular mortality. The results of most randomized studies indicate that interventional treatment of AF in patients with CHF and intermediate to low left ventricular ejection fraction (LV) contributes to reducing the functional class of CHF and improving quality of life, but at the same time, there is currently no consensus on the effectiveness, safety, and extent of catheter intervention. In this review, we attempted to summarize the literature data regarding the outcomes of interventional treatment of AF in patients with systolic LV dysfunction.

Key words: atrial fibrillation; chronic heart failure; low left ventricular ejection fraction; catheter ablation; pulmonary vein isolation

Conflict of Interests: none.
Funding: none.
Received: 20.03.2024 **Revision Received:** 25.09.2024 **Accepted:** 10.10.2024
Corresponding author: Khuziakhmetov Rustam, E-mail: rustam-huziahmetov@yandex.ru

R.D.Khuziakhmetov - ORCID ID 0009-0001-2835-9571, E.A.Shishkina - ORCID ID 0000-0001-6965-7869, B.K.Kadyraliev - ORCID ID 0000-0002-4007-7665, V.A.Belov - ORCID ID 0000-0002-0945-8208, S.N.Azizov - ORCID ID 0009-0006-1678-9175, O.V.Khlynova - ORCID ID 0000-0003-4860-0112

For citation: Khuziakhmetov RD, Shishkina EA, Kadyraliev BK, Belov VA, Azizov SN, Khlynova OV. Catheter ablation of atrial fibrillation in patients with systolic left ventricular dysfunction. *Journal of Arrhythmology.* 2024;31(4): e14-e21. https://doi.org/10.35336/VA-1356.

Atrial fibrillation (AF) is the most common arrhythmia among the adult population [1]. According to the EPOCHA study [2], AF is diagnosed in an average of 2.04% of the population. The prevalence of this arrhythmia increases significantly in older age groups and among individuals with concomitant cardiovascular pathology, reaching 12.3% in patients with chronic heart failure (CHF). Moreover, increasing life expectancy, improved diagnostic methods, and broader access to medical care are expected to result in a 2.3-fold increase in newly diagnosed cases of AF in the coming decades [1].

The prevalence of CHF, according to Russian studies in 2020, was 7% in the general population [3]. The EPOCHA-HF study indicated a growth in CHF prevalence from 6.1% to 8.2% over the past 20 years [4]. AF is a causative factor in the development of CHF in 12.3% of cases [4]. Furthermore, there is a well-established epidemiological link between AF and myocardial infarction (MI) [5], contributing to the development of CHF in patients with AF who have experienced MI. Shared risk factors and pathophysiological mechanisms underlying AF and CHF frequently result in their coexistence, which negatively affects disease progression and prognosis [6, 7].

Data from the RIF-HF multicenter registry, which studied the clinical course of CHF combined with AF and the prognostic significance of the arrhythmia [8], revealed that cardiovascular mortality and the risk of adverse outcomes over a one-year observation period varied significantly depending on the left ventricular ejection fraction (LVEF). Cardiovascular mortality in patients with CHF and AF was 4.1% in those with preserved LVEF (HFpEF), compared to 9.3% and 15.5% in patients with moderately reduced LVEF (HFmrEF) and reduced LVEF (HFrEF), respectively ($p<0.001$). The incidence of a composite endpoint (stroke, MI, cardiovascular death) was 22% and 25.5% in the HFmrEF and HFrEF groups, respectively ($p<0.001$) [8]. These findings underscore that AF in patients with left ventricular systolic dysfunction remains a pressing issue in modern healthcare.

According to current guidelines for the diagnosis and management of AF [1], catheter ablation with pulmonary vein isolation (PVI) is the first-line therapy for patients with AF and left ventricular dysfunction (Class I recommendation, Level of Evidence B). The results of most randomized studies, including PABA-CHF [9], Jones D. [10], CAMTAF [11], AATAC [12], CAMERA-MRI

[13], CASTLE-AF [14], CABANA [15], AMICA [16], and RAFT-AF [17], demonstrate that interventional treatment of AF in patients with left ventricular dysfunction contributes to reducing the functional class (FC) of CHF and improving quality of life. However, there is currently no consensus on the effectiveness, safety, and scope of catheter interventions.

The objective of the study is to summarise current literature on the outcomes of interventional treatment of AF in patients with left ventricular systolic dysfunction.

Ehe search and selection of publications on studies concerning the interventional treatment of AF in patients with chronic heart failure (CHF) were conducted using two databases: the Cochrane Library of Systematic Reviews (http://www.thecochranelibrary.com) and the Medline bibliographic database (http://www.ncbi.nlm.nih.gov/pubmed). Additional searches were performed using Google Scholar with the following keywords: atrial fibrillation, chronic heart failure, low ejection fraction, catheter ablation, pulmonary vein isolation. A total of 88 articles were analysed, resulting in a final list of 37 publications relevant to the review. Three key areas of focus were identified: the pathophysiological aspects of AF and CHF, the efficacy of radiofrequency ablation (RFA) of AF in patients with CHF, and the impact of interventional treatment of AF on the long-term prognosis of patients with AF and CHF.

PATHOPHYSIOLOGICAL ASPECTS OF AF AND CHF

Atrial fibrillation and CHF are two distinct nosological entities that can occur independently. However, they frequently develop concomitantly, as each condition can induce and perpetuate the other, forming so-called "vicious cycles" in pathogenesis. The interplay between AF and CHF is rooted in shared pathophysiological mechanisms. AF disrupts both systolic and diastolic cardiac functions, potentially leading to an increased incidence of CHF. Conversely, the structural and neurohormonal changes characteristic of CHF, whether with preserved or reduced LVEF, elevate the likelihood of AF onset and worsen disease prognosiser, AF and CHF share common risk factors-advanced age, arterial hypertension, diabetes mellitus, obesity, smoking, and sleep apnea syndrome-all of which independently raise the risk of developing both conditions (Figure 1)[18].

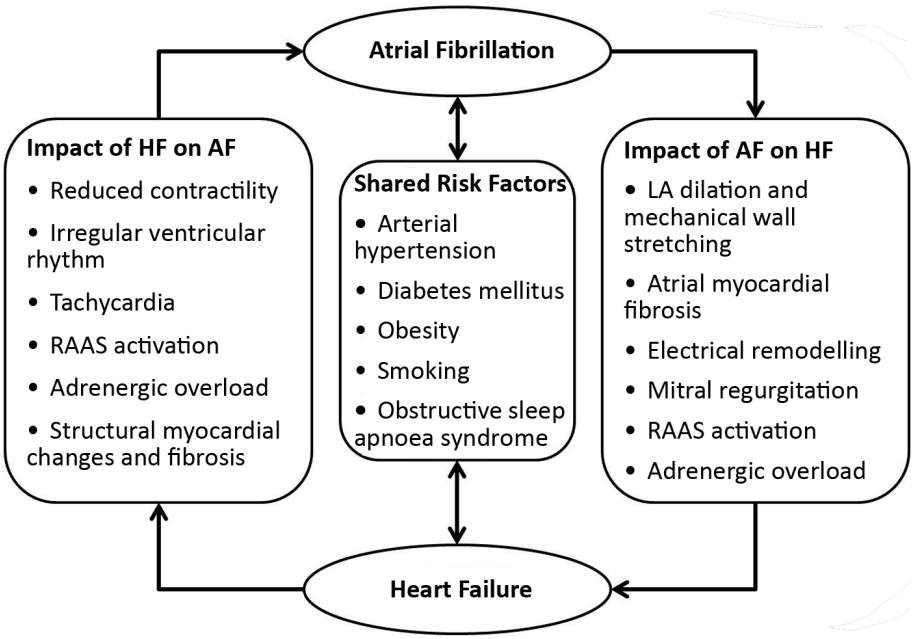

Figure 1. Pathophysiological relationship between atrial fibrillation and heart failure. Abbreviations: HF - heart failure; AF - atrial fibrillation; RAAS - renin-angiotensin-aldosterone system; LA - left atrium.

THE EFFECTIVENESS OF CATHETER ABLATION

Interventional treatment of AF has undergone significant advancements over a relatively short period, transitioning from atrioventricular node ablation (AVN) [19, 20] to standardized protocols for pulmonary vein isolation (PVI) [21] and high-density electroanatomical mapping [22]. Interest in interventional treatment of AF in patients with CHF began in 2004, with the publication of Michael S. Chen's study evaluating the efficacy and safety of catheter ablation of AF in patients with systolic LV dysfunction [23].

Between 2008 and 2022, 10 randomized clinical trials (RCTs) investigated the features of interventional treatment of AF in patients with CHF. These studies varied significantly in terms of average follow-up duration, ranging from 6 months in the PABA-CHF trial [9] to 4 years in the CAMERA-MRI [24] and CABANA [25] studies. Most trials focused on patients with persistent AF, such as the studies by M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], AATAC [12], CAMERA-MRI [13], and AMICA [16]. Patients with paroxysmal AF were included in PABA-CHF [9], CASTLE-AF [14], CABANA [15, 25], and RAFT-AF [17], with their proportion in the study groups ranging from 9% [17] to 49% [9].

The percentage of patients with ischemic etiology of CHF also varied considerably, with the lowest proportion (23%) in the CAMTAF study [11], 30–40% in RCTs by D.G. Jones (2013) [10] and RAFT-AF [17], over 40% in AMICA [16], and more than 60% in PABA-CHF [9] and AATAC [12]. The size of study groups also differed widely, from fewer than 50 participants in PABA-CHF [9], M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], and CAMERA-MRI [13], to 50–100 participants in AMICA [16] and CABANA [25], and more than 100 in AATAC [12], CASTLE-AF [14], and RAFT-AF [17]. The average LV ejection fraction (LVEF) in the study groups ranged from 18% (M.R. McDonald (2010) [26]) to 45% (CABANA [25]). Cardiac MRI was used to assess LVEF in the studies by M.R. McDonald (2010) [26], D.G. Jones (2013) [10], and CAMERA-MRI [13].

In addition to PVI, ablation strategies in these RCTs included non-pulmonary vein targets such as roofline ablation in the left atrium (LA), mitral isthmus, and posterior wall isolation. In PABA-CHF [9], CASTLE-AF [14], CABANA [25], AMICA [16], and RAFT-AF [17], the extent of non-pulmonary vein ablation was left to the operator's discretion. CAMERA-MRI [13] included posterior wall isolation along with PVI, while CAMTAF [11] used a strategy combining PVI with ablation of complex fractionated atrial electrograms (CFAEs), roofline, and mitral isthmus ablation. In AATAC [12], CFAE ablation was paired with roofline and superior vena cava isolation. D.G. Jones (2013) [10] implemented an extensive ablation strategy involving PVI, roofline, mitral isthmus, CFAE, and cavotricuspid isthmus ablation.

The operator's experience requirements also varied: a minimum of 50 procedures was required in CASTLE-AF [14] and 100 in CABANA [25]. Intervention standards included intracardiac echocardiography (PABA-CHF [9], AATAC [12]), general anesthesia (D.G. Jones (2013) [10], CAMERA-MRI [13]), and high-density mapping with a multipolar catheter (D.G. Jones (2013) [10]). AF recurrence was assessed using previously implanted intracardiac devices (CASTLE-AF [14]) or loop recorders implanted during catheter ablation (CAMERA-MRI [13]).

The duration of antiarrhythmic drug (AAD) therapy after catheter ablation varied, ranging from 4–6 weeks [13, 17] to 3–6 months [9, 12, 14]. In some cases, it continued beyond these periods if necessary. In the studies by D.G. Jones (2013) [10] and CAMTAF [11], AADs were discontinued immediately after ablation. Control groups across all RCTs included patients with AF and CHF who received medical therapy, with strategies focused on rate control (PABA-CHF [9], M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], CAMERA-MRI [13], RAFT-AF [17]), rhythm control (AATAC [12]), or optimal medical therapy (CASTLE-AF [14], CABANA [15, 25], AMICA [16]).

Comparison of Catheter Ablation for AF with Rate Control Strategies

The first RCT on this topic, PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure), was published in 2008 [9]. This study included 81 patients with AF and New York Heart Association (NYHA) Class II-III CHF (LVEF <40%). Participants were randomized into an intervention group (n=41) and a group receiving biventricular pacemaker implantation with subsequent AV node ablation (n=41). Six months post-intervention, 88% of patients in the catheter ablation group were free from AF (71% without antiarrhythmic drugs), with no progression to persistent AF (0% vs 30%, p<0.001), a greater 6-minute walk test distance (340 m vs 297 m, p<0.001), and improved LVEF (35% vs 28%, p<0.001). However, this was associated with a higher rate of perioperative complications (17%) compared to AV node ablation.

It is worth noting that earlier studies, such as RACE [27], AFFIRM [28], and AF-CHF [29], did not identify significant differences in mortality, quality of life, or stroke rates between rhythm control and rate control strategies with medication. However, the authors of PABA-CHF concluded that non-pharmacological treatment of AF is highly effective and superior to rate control via AV node ablation.

In 2010, a study by M.R. McDonald compared systolic LV function in patients with persistent AF and advanced CHF following interventional treatment (n=22) or pharmacological rate control (n=19) [26]. After 14 months, the success rate of interventional AF treatment was 50%. Unlike PABA-CHF, this study did not find significant differences in LVEF improvement (4.5% in the radiofrequency ablation (RFA) group vs 2.8% in the rate control group, p=0.6), nor in the 6-minute walk test or quality of life. The perioperative complication rate for RFA was 15% [26].

A similar study design was employed in the 2013 RCT by D.G. Jones, which included patients with persistent AF and CHF (LVEF <35%) randomized to catheter ablation (n=26) or pharmacological rate control (n=26) [10]. After 12 months, sinus rhythm was maintained in 88% of the catheter ablation group (including repeat procedures, 69% without antiarrhythmic drugs). The authors noted a trend toward improved 6-minute walk test distance (p=0.095) and myocardial contractility (LVEF +5.6%, p=0.055) following catheter ablation compared to rate control.

Further evaluation of rhythm control via RFA (n=26) and pharmacological rate control (n=24) in patients with persistent AF and systolic LV dysfunction (LVEF <50%) was conducted in the CAMTAF trial, published in 2014 [11]. After 6 months, the success rate of repeated interventions was 81%, with 38% success after a single procedure. At 12 months, 73% of patients remained AF-free without antiarrhythmic drugs. Unlike the studies by M.R. McDonald (2010) and D.G. Jones (2013), the CAMTAF trial reported significant LVEF improvement in the RFA group (from 32±8% to 40±12%), with no improvement in the rate control group (34±12% to 31±13%, p=0.015). Patients with sustained sinus rhythm experienced improved quality of life, though the perioperative complication rate for RFA reached 7.7%.

In 2017, results from the CAMERA-MRI trial (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) were published [13]. This study included patients with persistent AF and CHF (mean LVEF 33±8.6%), randomized to catheter ablation or pharmacological rate control. One month post-ablation, 75% of patients were AF-free (56% without antiarrhythmic drugs). At 6 months, both groups showed significant LVEF improvement (18.3% in the RFA group, p<0.001; 4.4% in the rate control group, p=0.0145). Substantial LVEF recovery (≥50%) was observed in 58% of the catheter ablation group compared to 9% in the rate control group (p<0.001). Catheter ablation was also associated with reverse LV remodeling (reduction in LV end-diastolic and end-systolic volumes) and left atrial volume. The authors concluded that catheter ablation significantly reduced NT-proBNP levels, improved exercise tolerance, NYHA class, and quality of life. The perioperative complication rate was 6%.

In 2020, long-term results of CAMERA-MRI were published [24]. Four years post-ablation, sinus rhythm was maintained in 43% of patients. LVEF improvement was significantly greater in the RFA group (16.4±13.3%) compared to the rate control group (8.6±7.6%, p=0.001).

In the RAFT-AF study, published in 2022, rhythm control with RFA (n=124) was compared to rate control (n=116) in patients with paroxysmal or persistent AF and CHF [17]. The minimum follow-up period was 2 years. The study found no significant difference in the primary endpoint (mortality and CHF decompensation) between groups (23.4% vs 32.5%, p=0.066). However, the RFA group demonstrated significantly improved LVEF (10.1±1.2% vs 3.8±1.2%, p=0.017), increased 6-minute walk test distance (44.9±9.1 m vs 27.5±9.7 m, p=0.025), better quality of life according to the Minnesota Living with Heart Failure Questionnaire (least squares mean difference: -5.4, 95% CI 1.7-10.7, p=0.0005), and greater reductions in NT-proBNP levels (mean change: -77.1% vs -39.2%, p<0.0001) [17].

Comparison of Catheter Ablation for AF with Rhythm Control Strategies

The AATAC (Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRT-D) randomized clinical trial (RCT), published in 2016, compared catheter ablation of AF (n=102) with amiodarone therapy (n=101) in patients with persistent AF and CHF (LVEF <40%) [12]. Unlike previous RCTs, which focused on comparing non-pharmacological rhythm control strategies with rate control (via medication or AV node ablation), this study assessed rhythm control efficacy through catheter ablation versus pharmacological intervention (amiodarone loading dose of 10 g over two weeks, followed by a maintenance dose of 200 mg). The mean follow-up period was 24 months. The study demonstrated higher efficacy of interventional treatment compared to amiodarone therapy (70% vs 37%, p<0.001), as well as significant reductions in all-cause mortality (8% vs 18%, p=0.037) and unplanned hospitalizations (31% vs 57%, p<0.001). The perioperative complication rate for catheter ablation was 8.1%.

Comparison of Catheter Ablation with Optimal Medical Therapy

Long-term outcomes of AF treatment were further evaluated in the multicenter CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial, published in 2018 [14]. This study enrolled patients with paroxysmal or persistent AF and NYHA class II-IV CHF (LVEF ≤35%), randomized to interventional treatment (n=179) or medical therapy (n=184, ~30% rhythm control, ~70% rate control). The average follow-up period was 37 months. The primary composite endpoint (death or hospitalization due to CHF decompensation) occurred significantly less often in the catheter ablation group compared to the medical therapy group (28.5% vs 44.6%, p=0.006). LVEF values increased by 8% after catheter ablation versus 0.2% with medical therapy after 60 months (p=0.005), and freedom from AF recurrence was achieved in 63.1% and 21.7% of patients, respectively (p<0.001). The perioperative complication rate was 7.8%.

The results of the multicenter CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial were published in 2019 [15]. This study compared catheter ablation (n=1108) with medical therapy (n=1096) in terms of efficacy and its impact on adverse outcomes (death, stroke, bleeding, or ventricular fibrillation/asystole). The median follow-up period was 48.5 months. No significant differences were observed between the groups for the primary composite endpoint (8.0% vs 9.2%, p=0.3). However, subgroup analysis of patients with CHF showed a 36% reduction in the primary endpoint (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.41–0.99) and a 43% reduction in all-cause mortality (HR 0.57, 95% CI 0.33–0.96) in the catheter ablation group compared to patients receiving medical therapy [25].

A 2019 study, AMICA, further evaluated catheter ablation of AF (n=68) versus optimal medical therapy (n=72) in patients with persistent AF and CHF (mean LVEF 28%) [16]. The authors did not find any significant advantages of catheter ablation over medical therapy after one year, primarily due to comparable increases in LVEF between the two groups (8.8% vs 7.3%, p=0.36)

IMPACT OF CATHETER ABLATION ON PROGNOSIS IN PATIENTS WITH AF AND CHF

Interest in interventional treatment for AF began in 2004 and primarily focused on evaluating efficacy, safety, and its impact on CHF progression (e.g., changes in left ventricular ejection fraction [LVEF], exercise tolerance, quality of life, and CHF functional class). Long-term outcomes were first reported in 2015 when T.J. Bunch et al. published a 5-year follow-up study of 267 patients with AF and CHF (LVEF ≤35%) after a single catheter ablation procedure for AF [30]. Comparison groups included patients with AF and CHF receiving medical therapy (n=1068) and patients with CHF without AF (n=1068). At the end of the 5-year follow-up, all-cause mortality rates were 27%, 55%, and 50%, respectively (p<0.001). The reduction in mortality in the catheter ablation group was attributed to lower cardiovascular mortality. Unlike most earlier studies, the authors did not observe significant differences in LVEF changes between the groups but identified a substantial reduction in CHF-related hospitalizations in the catheter ablation group. Additionally, T.J. Bunch et al**.** noted a trend toward fewer strokes in the catheter ablation group, although this difference was not statistically significant.

The AATAC randomized controlled trial (RCT) published in 2016 [12] also demonstrated lower mortality and fewer unplanned hospitalizations in the catheter ablation group compared to the amiodarone therapy group (8% vs. 18%, p=0.037; 31% vs. 57%, p<0.001, respectively) during the 2-year follow-up period.

The outcomes of adverse cardiovascular events and mortality in patients with AF and CHF after catheter ablation were published by J. Geng et al. in 2017 [31]. The catheter ablation group included 90 patients and was compared to a heart rate control group of 304 patients. The follow-up period was 13.5±5.3 months. Adverse cardiovascu-

lar events occurred significantly less often in the catheter ablation group (13.3% vs. 29.3%, p=0.005). The catheter ablation group also demonstrated lower rates of mortality, stroke, and unplanned hospitalizations compared to the rate control group (3.3% vs. 7.9%, 4.4% vs. 9.9%, and 10.0% vs. 16.1%, respectively), though these differences did not achieve statistical significance.

The study of mortality and CHF decompensation following catheter ablation compared to medical therapy was extended in the CASTLE-AF RCT [14]. Over a 37-month follow-up period, mortality rates were 13.4% and 25.0% (p=0.01), and hospitalization rates for CHF decompensation were 20.7% and 35.0% (p=0.004), respectively.

The results of observations in patients with AF and CHF (LVEF ≤45%) were published by S. Ichijo in 2018 [32]. Freedom from adverse events (death, stroke, or hospitalization due to CHF decompensation) at 1, 2, 3, and 4 years after the last intervention was 97.6%, 97.6%, 97.6%, and 88.7%, respectively. These findings highlight the significance of catheter ablation in managing patients with systolic left ventricular dysfunction and AF.

A review of current publications on interventional treatment of AF in CHF patients reveals that most authors report significant improvements in LVEF, CHF functional class (NYHA), quality of life, and exercise tolerance in patients with paroxysmal and persistent AF and CHF following CA [9-14, 16-17, 23-24, 32]. Several studies also demonstrated improved long-term outcomes, including reduced mortality and cardiovascular events, in this patient cohort [12, 14, 25, 30-32]. However, RCT found no advantages of CA over medical therapy in improving LVEF and CHF functional class [16, 26] or reducing long-term mortality [17].

The identification of predictors for LVEF improvement following interventional treatment of AF remains a pressing issue. A. Rillig et al. (2015) [33] and W. Ullah et al. (2016) [34] demonstrated the importance of sinus rhythm maintenance in improving LVEF. J. Kosiuk et al. (2014) [35] and M. Wang et al. (2017) [36] noted the greatest LVEF improvements in patients with the most severe systolic dysfunction. The CAMERA-MRI study [13, 24] identified the absence of myocardial fibrosis on gadolinium-enhanced cardiac magnetic resonance imaging as an independent predictor of LVEF improvement. R. Hunter et al. (2014) [11] reported that the absence of ischemic heart disease predicted better LVEF outcomes. Conversely, A. Pott et al. (2020) [37] found that pulmonary hypertension was a strong and independent predictor of LVEF non-improvement in patients with this condition (odds ratio [OR] 0.15, 95% confidence interval [CI] 0.041–0.540, p=0.004). However, these findings were not confirmed in other studies.

LVEF improvement is associated with various mechanisms of cardiac chamber remodeling. Sinus rhythm maintenance [33, 34] facilitates effective atrial systole, thereby increasing the overall left ventricular stroke volume. Tachycardia suppression optimizes atrial systolic contribution to ventricular filling, yielding the best outcomes at a heart rate of 50–80 beats per minute [18]. Additionally, the presence of viable myocardium [11, 13, 14] may be critically important for left ventricular remodeling and improved systolic function.

It is worth noting that no universally accepted model currently exists to predict LVEF changes after interventional treatment of AF in patients with systolic left ventricular dysfunction. The rate of intraoperative complications in this patient group remains a significant concern. The average complication rate in RCTs was 10.7%, ranging from 6% [13] to 17% [9].].

CONCLUSION

The appropriateness of interventional treatment for AF in patients with systolic left ventricular dysfunction is supported not only by existing publications but also by the current clinical guidelines for AF diagnosis and treatment. However, the data on the efficacy and safety of catheter ablation for AF, as well as on the optimal extent of lesion creation, vary significantly. This underscores the need for further research in this area.

In our view, it is particularly important to focus on identifying clinical predictors of perioperative complications and AF recurrence, determining risk factors for cardiovascular events in the long-term follow-up period, and developing a clinical model for selecting patients with systolic left ventricular dysfunction who are most likely to benefit from interventional treatment for AF while maintaining an acceptable risk of procedural complications. Establishing such a model would facilitate decision-making regarding the necessity of interventional procedures (including repeat interventions), taking into account the anticipated efficacy and long-term prognosis.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal* 2020;00:1-125. https://doi.org/10.1093/eurheartj/ehaa612.
2. Mareev YuV, Polyakov DS, Vinogradova NG, et al. Epidemiology of atrial fibrillation in a representative sample of the European part of the Russian Federation. Analysis of EPOCH-CHF study. *Kardiologiia*. 2022;62(4): 12-19 (In Russ.).
3. Russian Society of Cardiology (RSC) 2020 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology*. 2020;25(11): 4083 (In Russ.). https://doi.org/10.15829/1560-4071-2020-4083.
4. Polyakov DS, Fomin IV, Belenkov YuN, et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of follow-up? Results of the EPOCH-CHF study. *Kardiologiia*. 2021;61(4): 4-14 (In Russ.).
5. Shishkina EA, Khlynova OV, Lebedeva YI, et al. Atrial fibrillation and myocardial infarction: clinical-pathogenetic relationships and impact on prognosis. *Doctor.Ru.* 2023;22(8): 23-28 (In Russ.) https://doi.org/10.31550/1727-2378-2023-22-8-23-28.
6. Osmolovskaya YF, Romanova NV, Zhirov IV, et al. Epidemiology and management of heart failure patients with atrial fibrillation. *Medical Council*. 2016;(10): 93-97 (In Russ.).
7. Larina VN, Skiba IK, Skiba AS, et al. Heart failure and

atrial fibrillation: updates and perspectives. *Russian Journal of Cardiology*. 2022;27(7): 5018 (In Russ.).
8. Zhirov IV, Safronova NV, Osmolovskaya YuF, et al. Prognostic value of atrial fibrillation in patients with heart failure and different left ventricular ejection fraction: results of the multicenter RIF-CHF register. *Russian Journal of Cardiology*. 2021;26(1): 4200 (In Russ.).
9. Khan MN, Jaïs P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med.* 2008;359(17):1778-85. https://doi.org/10.1056/NEJMoa0708234.
10. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol.* 2013;61(18): 1894-903. https://doi.org/10.1016/j.jacc.2013.01.069.
11. Hunter RJ, Berriman TJ, Diab I et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol.* 2014;7(1): 31-8. https://doi.org/10.1161/CIRCEP.113.000806.
12. Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation*. 2016;133(17): 1637-44. https://doi.org/10.1161/CIRCULATIONAHA.115.019406.
13. Prabhu S, Taylor AJ, Costello BT, et al. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. *J Am Coll Cardiol.* 2017;70(16): 1949-1961. https://doi.org/10.1016/j.jacc.2017.08.041.
14. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med.* 2018;378(5):417-427. https://doi.org/10.1056/NEJMoa1707855.
15. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321(13): 1261-1274. https://doi.org/10.1001/jama.2019.0693.
16. Kuck KH, Merkely B, Zahn R, et al. Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial. *Circ Arrhythm Electrophysiol. 2019*;12(12): e007731. https://doi.org/10.1161/CIRCEP.119.007731.
17. Parkash R, Wells GA, Rouleau J, et al. Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial. *Circulation*. 2022;145(23): 1693-1704. https://doi.org/10.1161/CIRCULATIONAHA.121.057095.
18. Verhaert DVM, Brunner-La Rocca HP, van Veldhuisen DJ, et al. The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases. *Europace*. 2021;23(23 Suppl 2): ii40-ii45. https://doi.org/10.1093/europace/euaa368.
19. Gallagher JJ, Svenson RH, Kasell JH, et al. Catheter technique for closed-chest ablation of the atrioventricular conduction system. *N Engl J Med.* 1982;306(4): 194-200. https://doi.org/10.1056/NEJM198201283060402.
20. Scheinman MM, Morady F, Hess DS, et al.. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. *JAMA*. 1982;248(7): 851-5.
21. Phlips T, Taghji P, El Haddad M, et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace*. 2018;20(FI_3):f419-f427. https://doi.org/10.1093/europace/eux376.
22. Gasimova N.Z., Shabanov V.V., Safonov N.V., et al. Multipolar mapping in the management of different arrhythmias. *Journal of Arrhythmology.* 2024;31(1): 110-122 (In Russ.) https://doi.org/10.35336/VA-1297.
23. Chen MS, Marrouche NF, Khaykin Y, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic func-tion. *J Am Coll Cardiol.* 2004;43: 1004-1009.
24. Sugumar H, Prabhu S, Costello B, et al. Catheter Ablation Versus Medication in Atrial Fibrillation and Systolic Dysfunction: Late Outcomes of CAMERA-MRI Study. *JACC Clin Electrophysiol*. 2020;6(13): 1721-1731. https://doi.org/10.1016/j.jacep.2020.08.019.
25. Packer DL, Piccini JP, Monahan KH, et al. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. *Circulation*. 2021;143(14):1377-1390. https://doi.org/10.1161/CIRCULATIONAHA.120.050991.
26. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011;97(9):740-7. https://doi.org/10.1136/hrt.2010.207340.
27. Hagens VE, Crijns HJ, Van Veldhuisen DJ, et al. RAte Control versus Electrical cardioversion for persistent atrial fibrillation study group. Rate control versus rhythm control for patients with persistent atrial fibrillation with mild to moderate heart failure: results from the RAte Control versus Electrical cardioversion (RACE) study. *Am Heart J.* 2005;149(6): 1106-11. https://doi.org/10.1016/j.ahj.2004.11.030.
28. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol*. 2004;43(7):1201-8. https://doi.org/10.1016/j.jacc.2003.11.032.
29. Roy D, Talajic M, Nattel S, et al. Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358(25): 2667-77. https://doi.org/10.1056/NEJMoa0708789.
30. Bunch TJ, May HT, Bair TL, et al. Five-year outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction. *J Cardiovasc Electrophysiol.* 2015;26(4): 363-370. https://doi.org/10.1111/jce.12602.
31. Geng J, Zhang Y, Wang Y, et al. Catheter ablation versus rate control in patients with atrial fibrillation and heart failure: A multicenter study. *Medicine (Bal-*

timore). 2017;96(49): e9179. https://doi.org/10.1097/MD.0000000000009179.
32. Ichijo S, Miyazaki S, Kusa S, et al. Impact of catheter ablation of atrial fibrillation on long-term clinical outcomes in patients with heart failure. *J Cardiol.* 2018 Sep;72(3): 240-246. https://doi.org/10.1016/j.jjcc.2018.02.012.
33. Rillig A, Makimoto H, Wegner J, et al. Six-Year Clinical Outcomes After Catheter Ablation of Atrial Fibrillation in Patients With Impaired Left Ventricular Function. J Cardiovasc Electrophysiol. 2015;26(11): 1169-1179. https://doi.org/ 10.1111/jce.12765.
34. Ullah W, Ling LH, Prabhu S, et al. Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. *Europace*. 2016;18(5) :679-86. https://doi.org/10.1093/europace/euv440.
35. Kosiuk J, Nedios S, Darma A, et al. Impact of single atrial fibrillation catheter ablation on implantable cardioverter defibrillator therapies in patients with ischaemic and non-ischaemic cardiomyopathies. *Europace*. 2014;16(9): 1322-6. https://doi.org/10.1093/europace/euu018.
36. Wang M, Cai S, Ding W, et al. Efficacy and effects on cardiac function of radiofrequency catheter ablation vs. direct current cardioversion of persistent atrial fibrillation with left ventricular systolic dysfunction. *PLoS One.* 2017;12(3): e0174510. https://doi.org/ 10.1371/journal.pone.0174510.
37. Pott A, Jäck S, Schweizer C, et al. Atrial fibrillation ablation in heart failure patients: improved systolic function after cryoballoon pulmonary vein isolation. *ESC Heart Fail.* 2020;7(5):2258-2267. https://doi.org/10.1002/ehf2.12735.

https://doi.org/10.35336/VA-1435

UNUSUAL FINDINGS DURING TRANSESOPHAGEAL ELECTROPHYSIOLOGY STUDY

M.M.Medvedev
North-West Center for Diagnostics and Treatment of Arrhythmias, Russia, Saint Petersburg, 40 Lunacharsky ave., buil. 4.

The article presents the results of a transesophageal electrophysiological study of a 39-year-old patient with a combination of an accessory pathway and dissociation of the atrioventricular node into fast and slow conduction zones. The criteria for identifying slow anterograde conduction along the accessory pathway and a rare mechanism for inducing paroxysmal reciprocal atrioventricular nodal tachycardia are discussed.

Key words: transesophageal electrophysiology study; accessory pathways; Wolff-Parkinson-White syndrome; dissociation of the atrioventricular node into fast and slow conduction zones; double atrioventricular conduction; paroxysmal reciprocal atrioventricular nodal tachycardia

Conflict of Interest: none.
Funding: none.
Received: 29.10.2024 **Revision received:** 09.11.2024 **Accepted:** 21.11.2024
Corresponding author: Medvedev Mikhail, E-mail: mikhmed@mail.ru

M.M.Medvedev - ORCID ID 0000-0003-4903-5127

For citation: Medvedev MM. Unusual findings during transesophageal electrophysiology study. *Journal Arrhythmology.* 2024;31(4): e22-e30. https://doi.org/10.35336/VA-1435.

The examination and treatment of patients with the Wolff-Parkinson-White (WPW) phenomenon and syndrome have been extensively documented in numerous publications. In recent years, particular attention has been focused on the non-invasive and invasive risk assessment of patients with manifest, intermittent, and latent WPW phenomenon [1-3]. We have published a series of observations highlighting the potential of transesophageal (TE) electrophysiological study (EPS) in the risk stratification of patients with WPW phenomenon and syndrome [4, 5]. One such observation discusses the validity of diagnosing WPW phenomenon in a patient whose ventricular dyssynchrony, associated with the presence of an accessory pathway (AP), resulted in a marked reduction in the left ventricular ejection fraction (LVEF) [5].

In patients with WPW syndrome (or those with concealed APs exhibiting only retrograde conduction), the occurrence of paroxysmal tachycardia in early adulthood is more typical compared to patients with zones of fast and slow conduction in the atrioventricular (AV) node. Thus, knowing the onset age of palpitations in a patient allows us to preliminarily hypothesize the anatomical substrate responsible. However, exceptions to this rule undoubtedly exist. Below, we present the results of a TE EPS.

A 39-year-old patient, G., sought medical care at the North-West Center for Diagnostics and Treatment of Arrhythmias. The primary reason for the visit was to adjust antihypertensive therapy. During anamnesis collection, it was revealed that the patient had been experiencing brief episodes of rhythmic palpitations with sudden onset and termination since childhood. These episodes were self-terminated or resolved using vagal maneuvers but had never been captured on an electrocardiogram (ECG) or Holter ECG monitoring. As a result, the patient was advised to undergo a TE EPS.

Before initiating TE EPS, the patient presented with sinus tachycardia at a heart rate of 90-105 bpm. The P-wave width was 100 ms, the PQ interval measured 150 ms, the QRS complex width was 90 ms, and the QT interval duration was 350 ms (Figure 1). A contour analysis revealed smoothing of the ascending segment of the R wave in leads V4-V5 (where the onset of the QRS complex was most distinct), the presence of a broad Q wave in lead III, and an almost isoelectric onset of the QRS complex (lasting up to 10 ms) in the right precordial leads. This isoelectric initiation of the QRS complex in certain precordial leads may suggest that ventricular excitation begins from a single focal point rather than multiple areas within the Purkinje fiber distribution. Such an initial depolarisation pattern is typically observed in ventricular ectopy or anterograde conduction along an AP.

Clearly, the patient did not exhibit the "classic" Wolff-Parkinson-White syndrome, as evidenced by a normal PQ interval, absence of a delta wave, normal QRS complex width, and unaltered repolarisation. However, this pattern may occur in the presence of a slow-conducting accessory pathway, where excitation via the AP engages only a very small portion of the ventricular myocardium. The criteria for identifying such APs were detailed in a prior study [6]. In that work, the authors used coherent summation of QRS complexes—traditionally applied to detect late ventricular potentials—to identify low-amplitude potentials preceding the QRS onset and developed quantitative criteria for diagnosing "concealed anterograde conduction via an AP."

We also employed the late ventricular potential analysis option to investigate signs of anterograde conduction via an AP in this patient. The results are presented in Figure 2. In lead X (Frank lead system), the very gradual onset of the QRS complex is clearly visible, and in leads Y and Z, low-amplitude potentials, corresponding temporally to the start of the QRS complex, can be observed. These can be interpreted as equivalents of a minimally expressed delta wave. The delta wave is most distinct in the filtered QRS complex. Thus, ECG analysis using the coherent summation method suggested the presence of an AP with slow anterograde conduction in this patient. This hypothesis, of course, required further confirmation.

Before initiating transesophageal cardiac stimulation (TECS), a transesophageal ECG was recorded and displayed instead of lead V3. The P waves on the transesophageal ECG were of considerable amplitude and biphasic in nature (Figure 3). The sinus node recovery time, determined using orthorhythmic stimulation at a frequency of 150 impulses/min, voltage of 14 V, and pulse duration of 20 ms, was measured at 900 ms, with a corrected value of 250 ms (Figure 4). It is essential to note that the Holter ECG system used to record

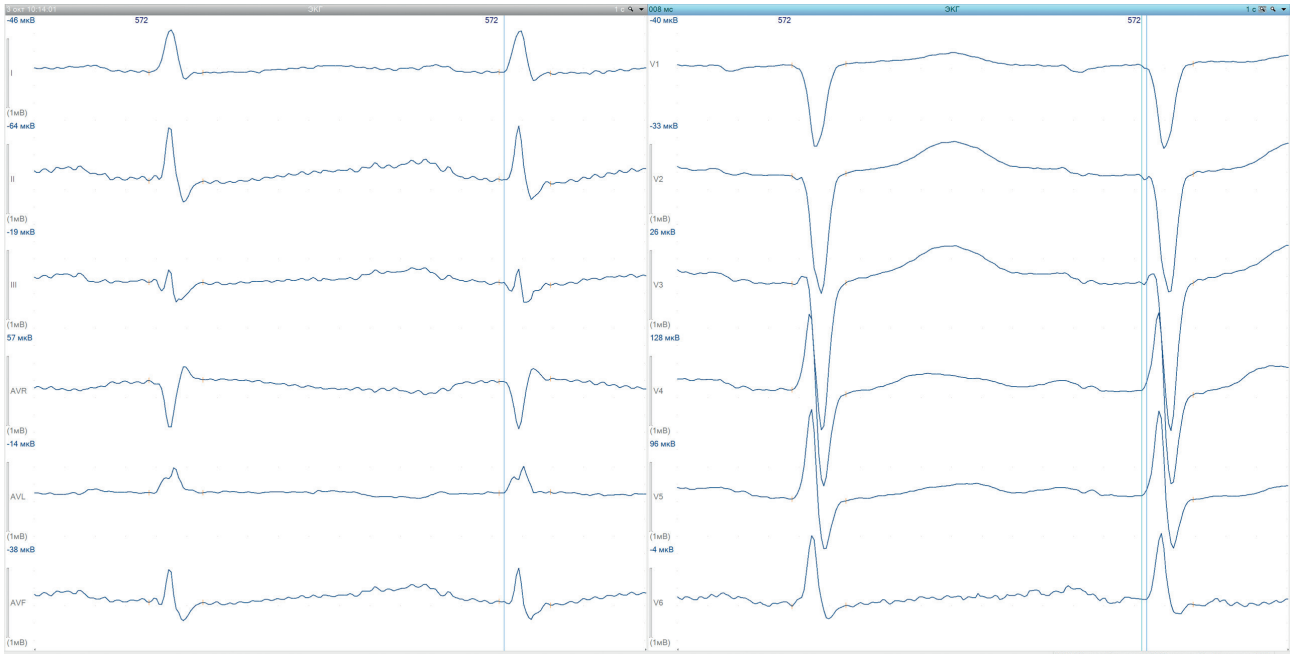

Figure 1. Fragment of Holter ECG monitoring of patient G. in the standard twelve leads, recorded prior to the study. Explanations in the text.

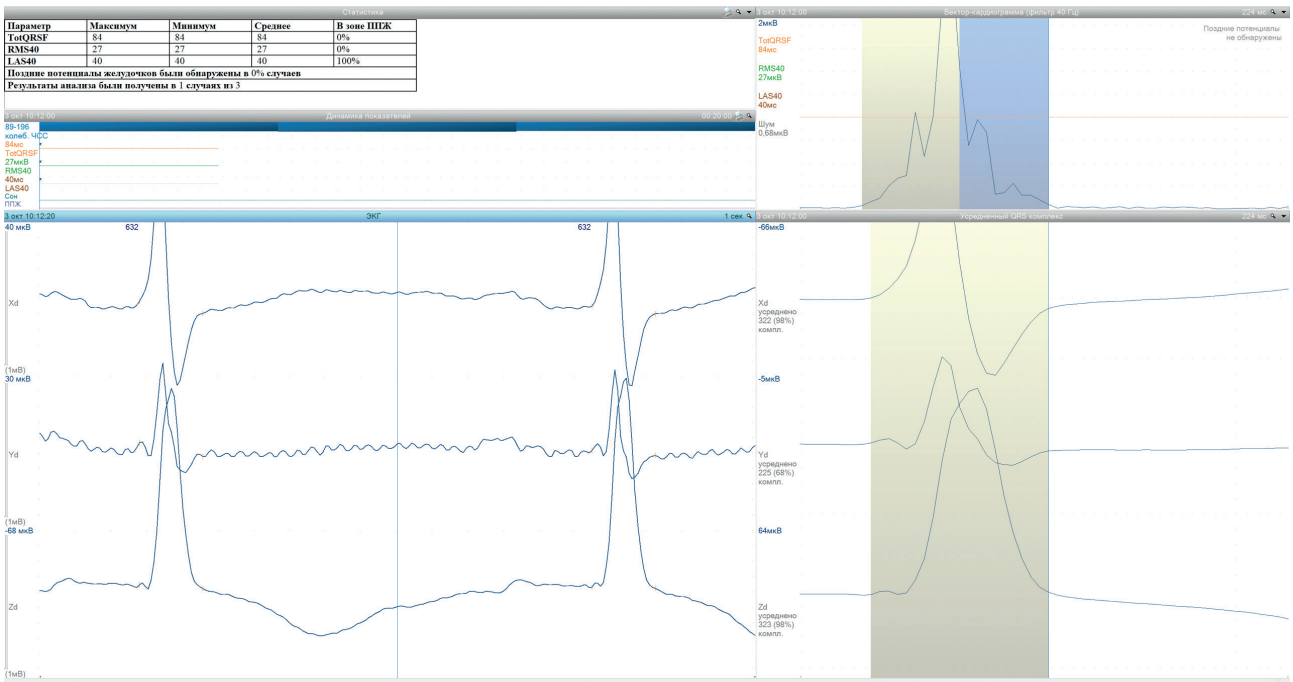

Figure 2. Application of the ventricular late potential detection option to identify signs of anterograde conduction via the accessory pathway (AP) in patient G. The Frank leads are shown (bottom left), along with the result of coherent averaging of QRS complexes (225 to 323 complexes) until the required noise level was achieved (bottom right), and the filtered QRS complex (top right). Explanations in the text.

the cardiac signal is not designed for transesophageal electrophysiology study (TE EPS) data analysis. Consequently, it may incorrectly classify TECS impulses as QRS complexes. Therefore, the numerical results should be interpreted with caution, and particular attention should be paid to the placement of small red markers indicating where the system identified the start and end of QRS complexes or stimulation impulses.

During programmed TECS, the basic rhythm was set at 100 impulses/min, with a testing impulse delay of St1-St2 = 340 ms, St1-R1 interval = 200 ms, and St2-R2 interval = 260 ms (Figure 5). The QRS complex induced by the testing impulse was significantly different from both the basic stimulation QRS complexes and the spontaneous sinus rhythm QRS complexes. Notably, the QRS complex no longer exhibited even minimal signs of pre-excitation. This was most evident in lead V3, where the R-wave amplitude tripled. This absence of anterograde conduction via the AP can serve as a diagnostic criterion in further analysis. It is crucial to highlight that the effective refractory period (ERP) of the AP was at least 340 ms. Further prolongation of the testing impulse delay was not conducted, as it was unlikely to influence therapeutic strategies.

When the testing impulse delay was reduced in 10 ms increments to 300 ms, the St2-R2 interval increased to 270 ms, and an echo beat was observed with an RR interval of 330 ms (Figure 6). A retrograde P' wave of sufficient width and negative polarity was clearly visible in the inferior

Figure 3. Registration of the transesophageal electrogram of patient G. (displayed in place of lead V3). Explanations in the text.

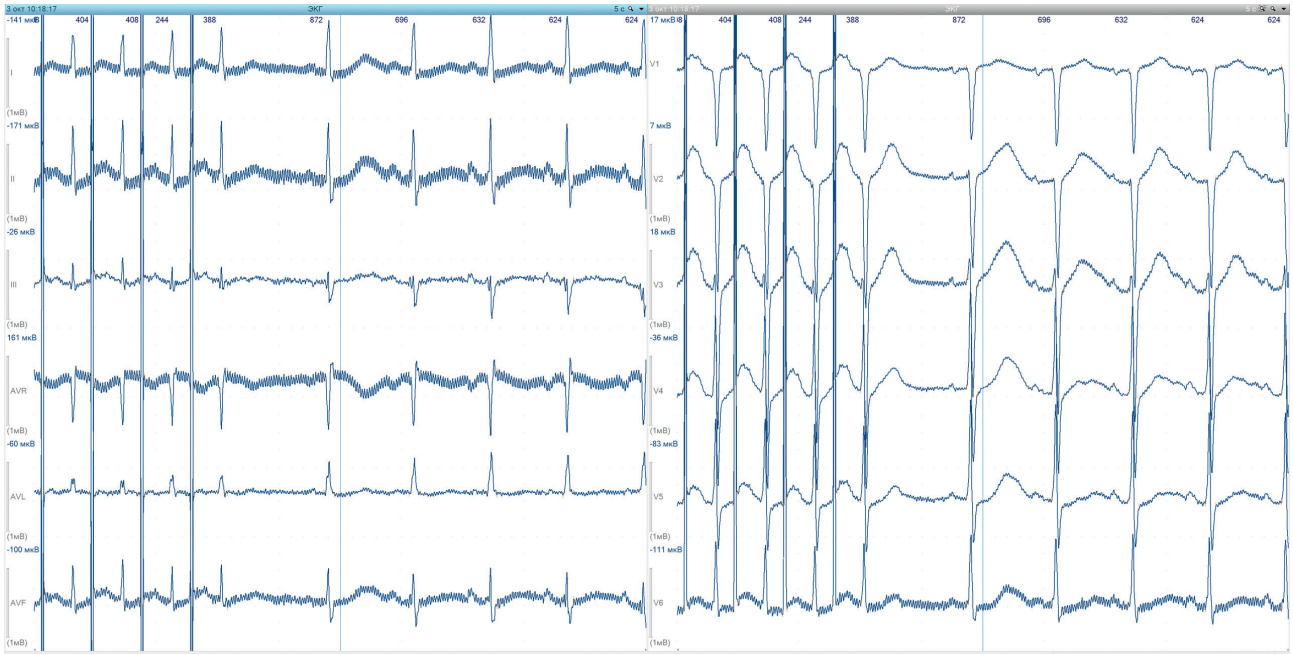

Figure 4. Conducting orthorhythmic cardiac pacing (CP) for determining the sinus node recovery time in patient G. Explanations in the text.

leads, with an RP' interval of approximately 120 ms. This indicates that the testing impulse was conducted through the AV node without AP involvement (as the AP was in a refractory state) and subsequently spread retrogradely to the atria via the AP, which had exited its refractory period. The RR interval of 330 ms suggests the theoretical possibility of inducing paroxysmal orthodromic reciprocating AV tachycardia with a rate of approximately 180 bpm.

When the St1-St2 interval was reduced to 290 ms, the St2-R2 interval increased to 280 ms, and no echo beats were observed. A subsequent reduction in the testing impulse delay to 280 ms resulted in the induction of tachycardia comprising four narrow QRS complexes (Figure 7). The tachycardia rate exceeded 200 bpm, and no distinct retrograde P waves were visible. This raised the possibility of paroxysmal AV nodal reciprocating tachycardia (AVNRT). Typically, AVNRT is induced when a testing impulse conducts to the ventricles via the slow AV node pathway and returns to the atria via the fast pathway, completing a re-entry loop. However, in this case, such a mechanism was excluded because the St2-R2 interval was 300 ms, and its prolongation with decreasing testing impulse delays occurred gradually without abrupt jumps or discontinuities in the AV conduction curve.

An alternative mechanism for AVNRT induction involves double AV conduction, where a single P wave or stimulation impulse produces two QRS complexes due to conduction via both the fast and slow AV node pathways. This induction mechanism has been previously documented during endocardial electrophysiology studies [7]. It appears that this was the mechanism observed in this patient. Supporting this interpretation are pseudo-Q waves in the

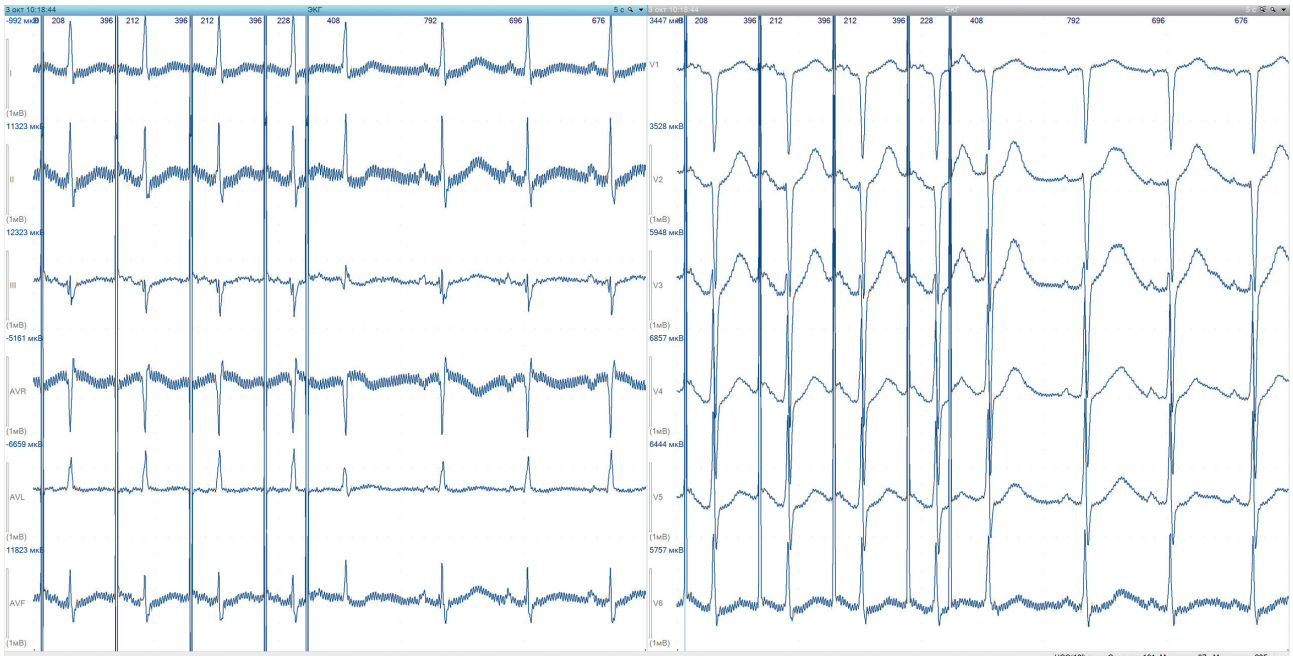

Figure 5. Result of programmed CP in patient G. with a test stimulus delay of 340 ms. Explanations in the text.

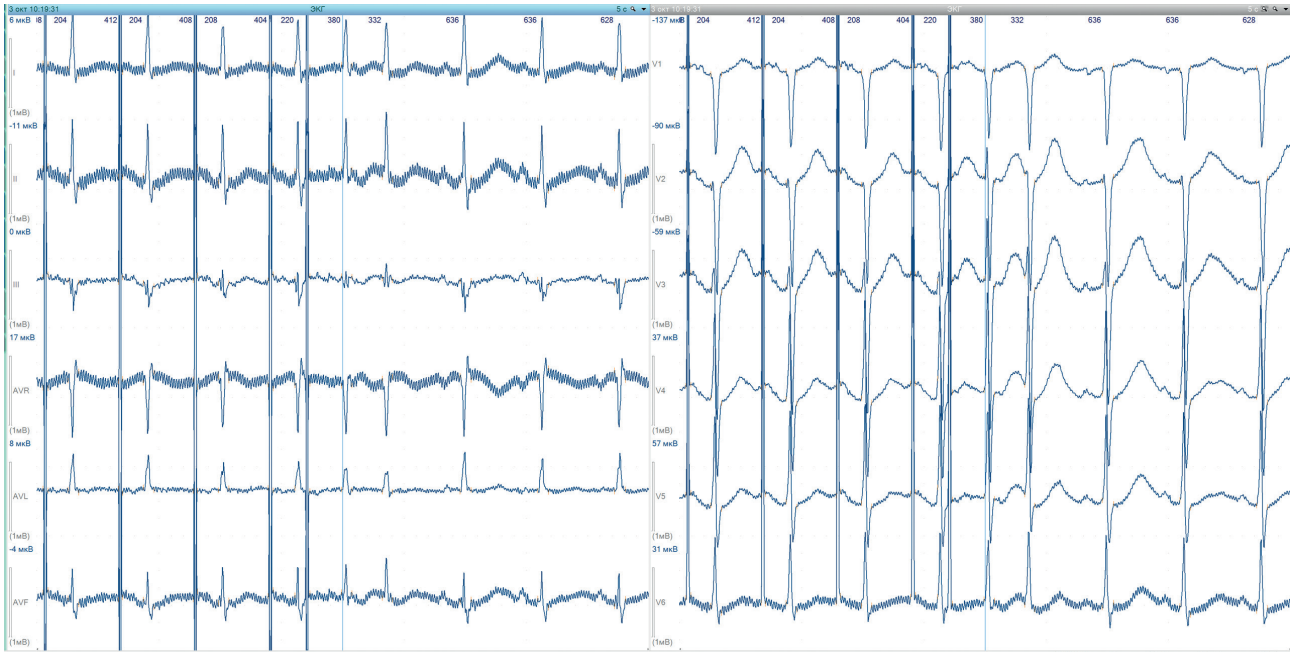

Figure 6. Result of programmed CP in patient G. with a test stimulus delay of 300 ms: recording of an echo beat. Explanations in the text.

second to fourth QRS complexes of the tachycardia, most prominently visible in lead V3. These pseudo-Q waves are, in fact, narrow retrograde P' waves originating from the AV node and propagating concentrically through the atria. Their position preceding the QRS complex (negative RP' interval) indicates that re-entry excitation conducts retrogradely faster than anterogradely.

This tachycardia pattern, characterized by four narrow QRS complexes, was also observed during programmed TECS with testing impulse delays ranging from 280 to 260 ms. This establishes the presence of a tachycardia zone between 290 and 260 ms, although the nature of the tachycardia requires further clarification via transesophageal ECG recording and RP' interval assessment. At an St1-St2 interval of 250 ms, the ERP of the AV node was reached.

During Wenckebach point determination (Figure 8), the value was measured at 220 impulses/min, inducing a brief tachycardia episode exceeding 200 bpm with wide QRS complexes characteristic of complete right bundle branch block. In the figure, the left blue arrow marks an impulse that failed to conduct to the ventricles, while the right arrow indicates an impulse that induced tachycardia, likely through double conduction. A transesophageal ECG recording during tachycardia was not obtained (the red arrow indicates electrode V3 disconnection).

By manually delivering three impulses, we induced a sustained paroxysm of tachycardia (Figure 9). The mechanism of tachycardia induction appears to follow the "classic" pattern: the second impulse propagated via the fast conduction zone of the AV node, while the third impulse

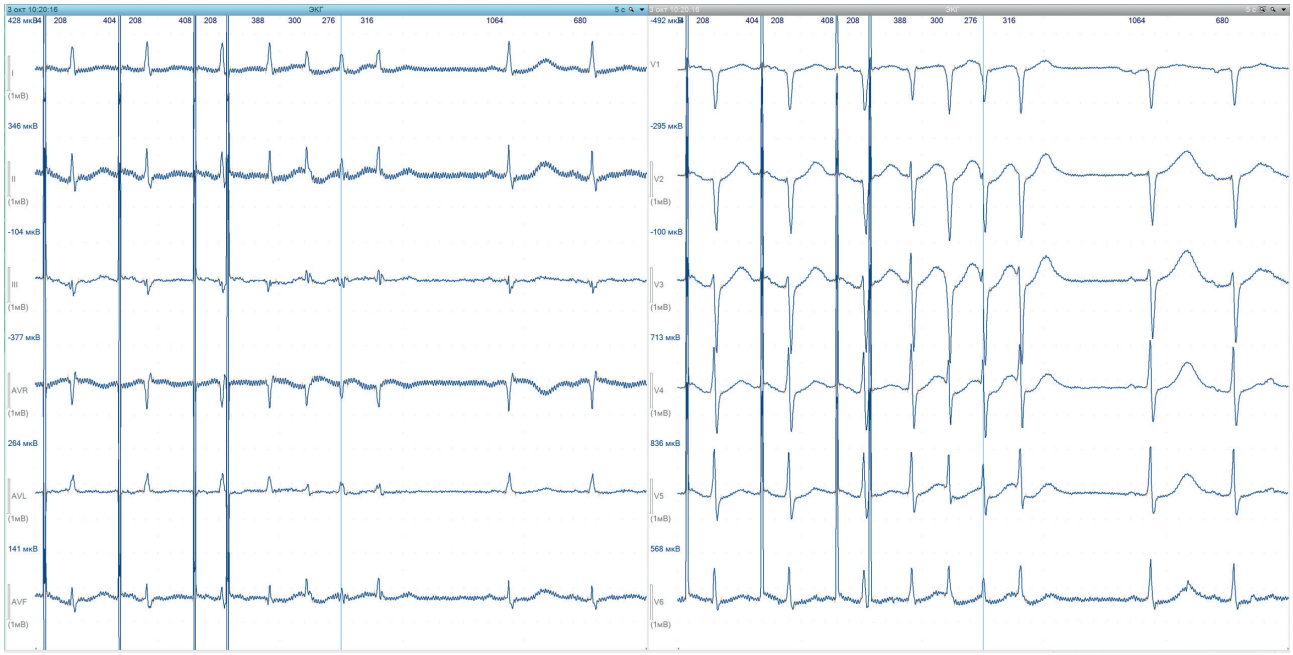

Figure 7. Result of programmed CP in patient G. with a test stimulus delay of 290 ms: induction of tachycardia comprising four QRS complexes. Explanations in the text.

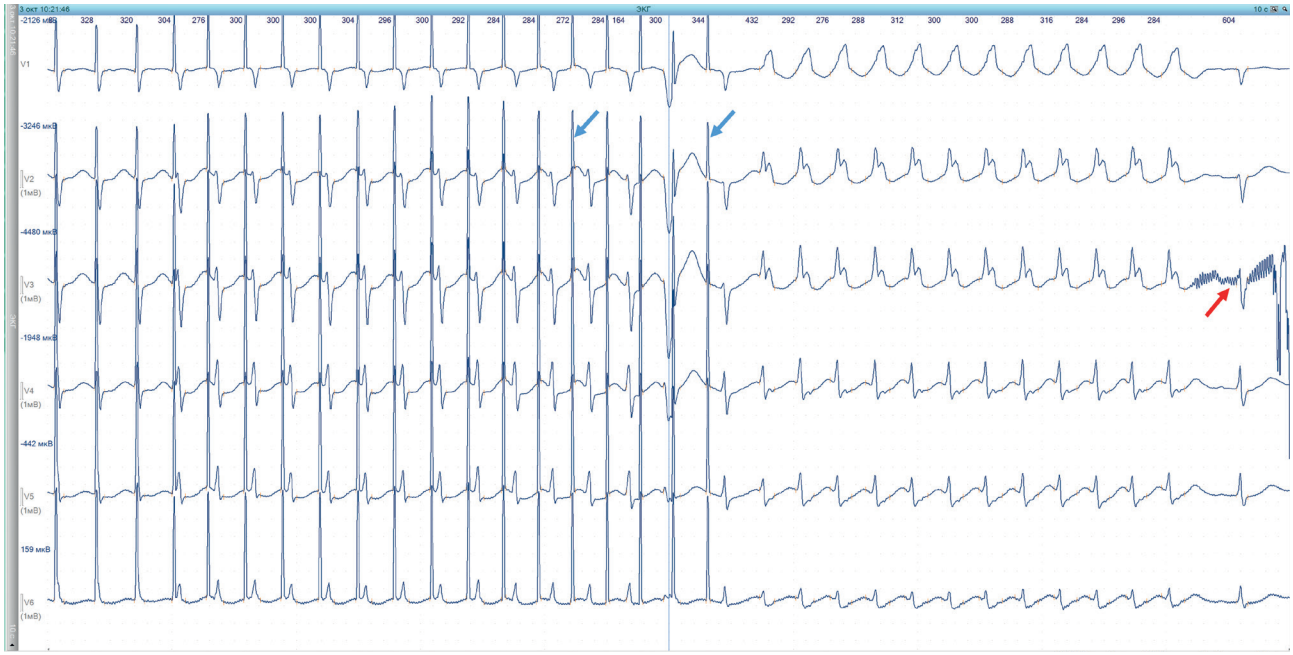

Figure 8. Result of Wenckebach point determination in patient G.: induction of tachycardia with a pattern of complete right bundle branch block (RBBB) at a frequency exceeding 200 bpm. Explanations in the text.

conducted via the slow conduction zone, completing the re-entry loop. An unusual signal morphology was noted in lead V3, which resulted from its disconnection. This was intentionally left disconnected to allow for a quicker recording of the TE ECG in the event of short paroxysms.

The induced paroxysm, with a right bundle branch block (RBBB) pattern, was sufficiently prolonged to permit the recording of a TE ECG (Figure 10). The RP' interval (noted in lead V3) measured 60 ms, confirming the diagnosis of paroxysmal reciprocating AVNRT. Interestingly, attempts to terminate the paroxysm using TECS were unsuccessful, necessitating the administration of adenosine triphosphate (ATP) to restore sinus rhythm.

Given the tachycardia rate exceeding 200 bpm, a rapid intravenous administration of 20 mg ATP was performed (Figure 11). The final event in the tachycardia sequence was marked by a P' wave, followed by a ventricular extrasystole with retrograde conduction to the atria (RP' interval = 160 ms), after which sinus rhythm resumed with AV conduction block. The maximum RR interval reached 4600 ms, which was asymptomatic. The rhythm strip displaying TE ECG illustrates that during ATP action, conduction initially propagated through the AV node's slow pathway (PQ interval = 260 ms), transitioning sharply to the fast pathway (PQ interval = 160 ms). This abrupt shift may have been influenced by retrograde conduction to the atria. Sinus node discharge and the subsequent increase in the RR interval from 600 to 770 ms facilitated the resumption of anterograde conduction through the fast AV nodal pathway, corroborat-

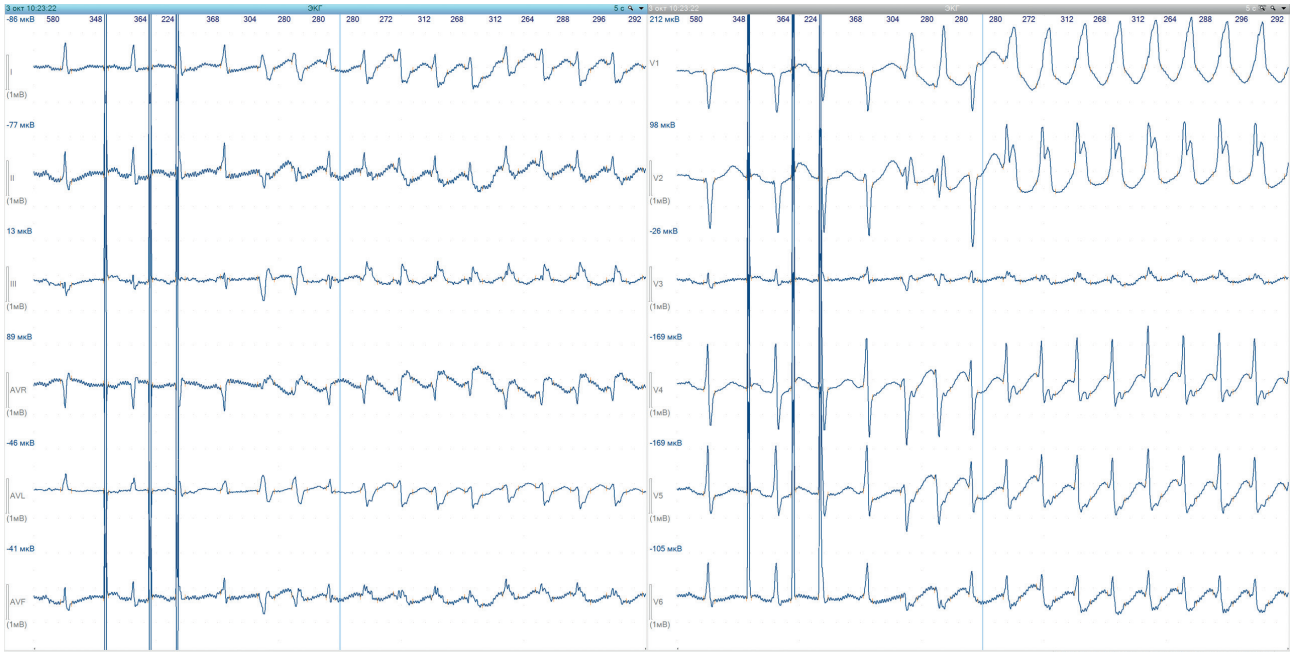

Figure 9. Induction of tachycardia with an RBBB pattern by delivering three impulses in manual mode. Explanations in the text.

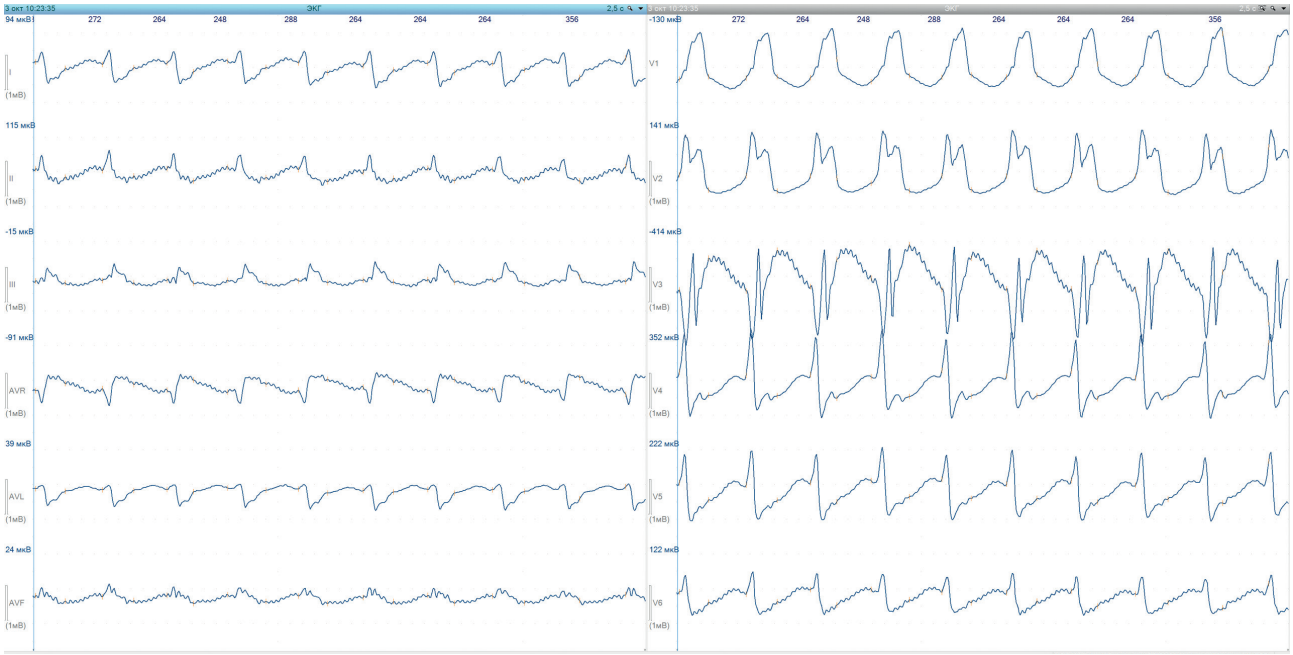

Figure 10. Registration of the transesophageal electrogram of patient G. during tachycardia (displayed in place of lead V3). Explanations in the text.

ing the presence of both fast and slow conduction zones within the AV node.

After the restoration of sinus rhythm via ATP administration, ST segment depression exceeding 200 μV was observed, most prominently in leads V4 and V5 (Figure 12). It is well-documented that ATP can cause a coronary steal phenomenon in patients with fixed coronary obstruction. This finding underscores the importance of thorough clinical evaluation, including stress echocardiography, to assess the patient's coronary status comprehensively.

Thus, the results of the TE EPS conducted on patient G., whose anamnesis suggested the presence of a concealed accessory pathway (AP) and paroxysmal reciprocating orthodromic AV tachycardia, revealed not only the concealed AP but also the existence of fast and slow conduction zones in the AV node. Anterograde conduction via the AP with minimal ventricular involvement was demonstrated, confirmed by the recording of ventricular late potentials and the dynamic assessment of QRS complex morphology during programmed cardiac stimulation.

AVNRT was induced at a rate exceeding 200 bpm and was terminated by administering 20 mg of ATP. A rare mechanism of tachycardia induction was identified, along with indirect signs that allowed its characterization prior to TE ECG recording. The patient was referred for radiofrequency catheter ablation of the slow pathway zone in the AV node.

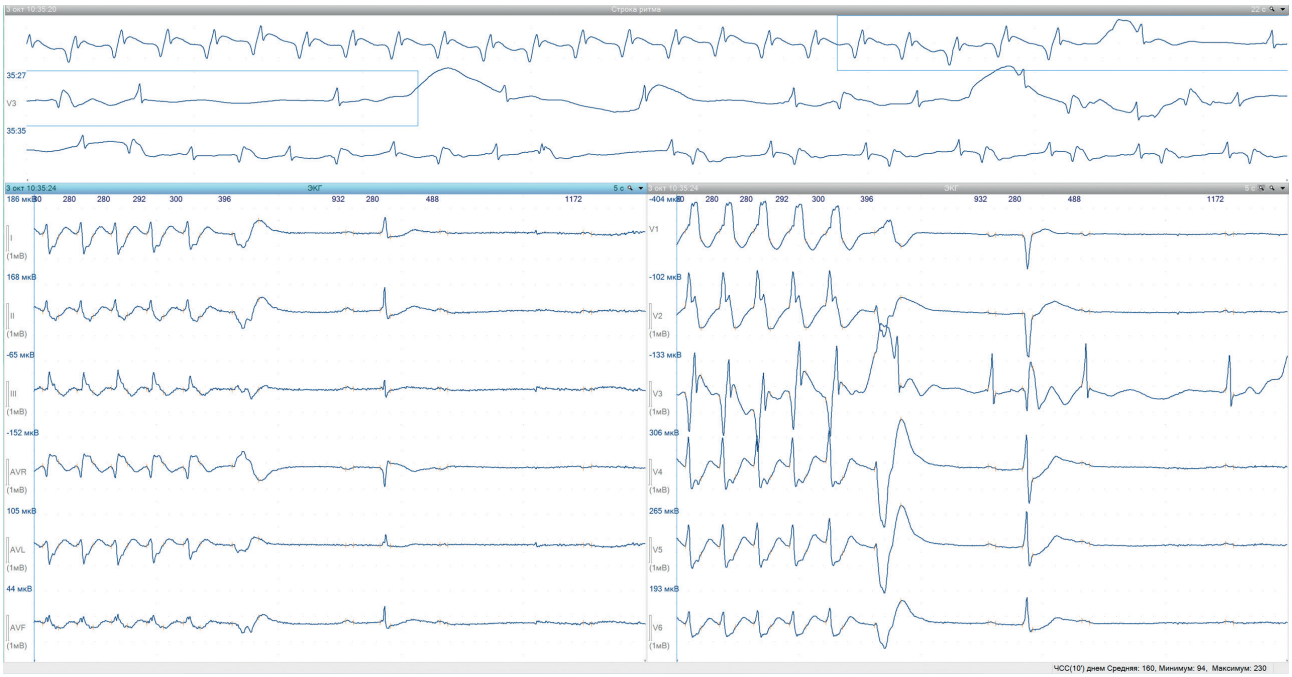

Figure 11. Registration of sinus rhythm restoration after intravenous bolus administration of 20 mg adenosine triphosphate (ATP). The rhythm strip (top) shows the transesophageal electrogram. Explanations in the text.

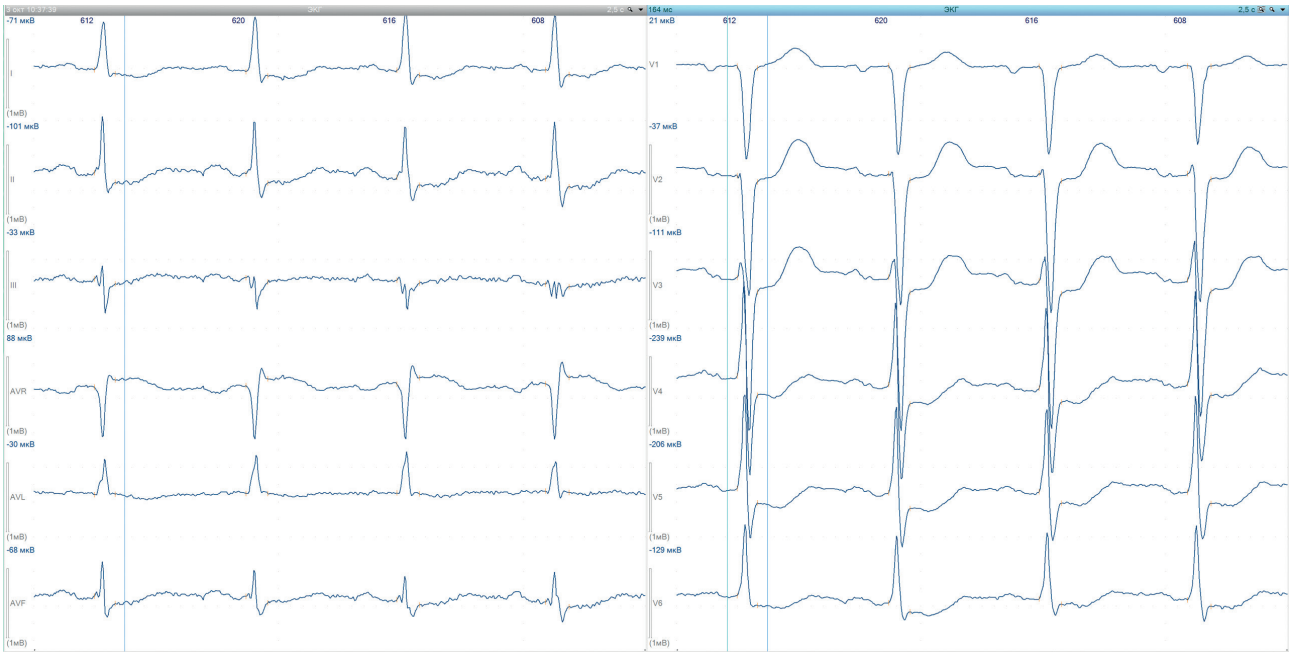

Figure 12. Assessment of ST-segment depression in patient G. following sinus rhythm restoration. Explanations in the text.

RFEFERENCES

1. Obeyesekere MN, Leong-Sit P, Massel D, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. *Circulation* 2012;125: 2308-15. https://doi.org/10.1161/CIRCULATIONAHA.111.055350.

2. Pappone C, Santinelli V, Rosanio S, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. *J Am Coll Cardiol*. 2003;41: 239-44. https://doi.org/10.1016/S0735-1097(02)02706-7.

3. Kiger ME, McCanta AC, Tong S, et al. Intermittent versus Persistent Wolff-Parkinson-White syndrome in children: electrophysiologic properties and clinical outcomes. *Pacing Clin Electrophysiol.* 2016;39: 14–20. https://doi.org/10.1111/PACE12732.

4. Rivin AE, Gordeeva MV, Sokurenko NS, Medvedev MM. Revisited properties of accessory pathways. *Journal of arrhythmology.* 2015;79: 70-72(In Russ.)

5. Savelev AA, Kamenev AV, Berman MV, Medvedev MM. Examination and treatment of a female patient with symptomatic manifesting WPW phenomenon: case report. *Journal of Arrhythmology.* 2022;29(4): e1-e8(In Russ.) https://doi.org/10.35336/VA-2022-4-11.

6. Katoh T, Ohara T, MD; Kim EM, Hayakawa H. Non-invasive diagnosis of concealed Wolff-Parkinson-White syndrome by detection of concealed anterograde pre-excitation. *Jpn Circ J.* 2001;65: 367-370.

7. Al Mehairi M, Al Ghamdi SA, Dagriri K, Al Fagih A. Simultaneous antegrade dual AV node conduction initiates AV nodal re-entrant tachycardia (a rare initiation mechanism). *Journal of the Saudi Heart Association*. 2013;25(1): 35-37. https://doi.org/10.1016/j.jsha.2012.07.005.